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Plant derived alkaloids in major neurodegenerative diseases: from animal models to clinical trials

Shikha Girdhar[1], Amit Girdhar[2], Santosh Kumar Verma[3], Viney Lather[2], Deepti Pandita[4]

1 *Department of Pharmacology, JCDM College of Pharmacy, Barnala Road, Sirsa-125055, India*
2 *Department of Pharmaceutical Chemistry, JCDM College of Pharmacy, Barnala Road, Sirsa-125055, India*
3 *Department of Pharmacology, CT Institute of Pharmaceutical Sciences, Jalandhar-144020, India*
4 *Department of Pharmaceutics, JCDM College of Pharmacy, Barnala Road, Sirsa-125055, India*

ABSTRACT

Alzheimer's disease (AD) and Parkinson's disease (PD) are two most common neurodegenerative diseases that primarily target the elderly population in society. The global economic and social burden of these neurodegenerative diseases is very high. To date, available treatments for these diseases are based on the neurotransmitter modulation and provide only symptomatic benefit. There is an urgent need to find the more effective treatments which can alter the underlying pathology of neurodegenerative diseases and stop their rising prevalence. Although many disease modifying approaches are under investigation, yet there is no successful candidate in market. Further, the current therapies focus on single target. However, the diseases like AD and PD which have complex pathology can be better controlled if we opt for a multi-targeted approach. In view of this, treatment by plant-derived alkaloids themselves or their derivatives is a promising hope. The aim of this review is to discuss the current progress with respect to clinical research, in development of alkaloids primarily obtained from plants and their derivatives for treatment and delay of these two devastating disorders. Also, the various mechanistic approaches of plant-derived alkaloids are highlighted..

Keywords: Acetylcholinestrase inhibitors, Alzheimer's disease, clinical trials, Plant-derived alkaloids, Parkinson's disease.

INTRODUCTION

The two most common age-related neurodegenerative disorders; Alzheimer's and Parkinson's diseases, account for a significant and increasing proportion of morbidity and mortality in the developed world [1]. These are chronic and progressive conditions associated with long-term care, suffering, and lost quality of life. Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder of the brain characterized clinically by impairment of multiple cognitive functions. It is the major cause of dementia and accounts for 60–80% of cases in elderly [2]. After AD diagnosis, since the patient may live for more than a decade, it is also a leading cause of disability in the elderly. The cases of AD diagnosed each year in USA alone are expected to increase to 13.2 million by 2050 [3]. The most common pathological features identified in AD brains are the presence of intracellular neurofibrillary tangles (NFTs) and extracellular amyloid plaques [4]. The cleavage of amyloid-β peptide from neuronal transmembranous amyloid precursor protein (APP) results in formation of amyloid plaques. Two proteases named, β-secretase and γ-secretase catalyze this cleavage sequentially. Depending upon the site of γ-secretase cleavage, there is formation of either less toxic Aβ38-40 peptide (more than 95%) or more toxic and highly aggregating Aβ42 peptide (less than 5%). Amyloid plaques are formed by the accumulation of Aβ42 followed by aggregation, oligomerization, and fibril and proto-fibril formation. Further there is cascade of events like inflammation, free radical formation, oxidative stress and hyperphosphorylation of tau proteins to form NFTs. This results in neurotransmitter dysfunction, excitotoxicity and neuronal death [5]. These changes occurring in the association area of the cerebral cortex, the hippocampus and the middle and temporal lobes are accompanied by decreased concentrations of the neurotransmitter acetylcholine (ACh). The loss of cholinergic function in AD is believed to be responsible for much of the short-term memory deficit. The excitatory neurotransmitter, glutamate also plays an important role in learning and memory. Studies have shown that there is a slow glutamate excitotoxicity in AD which leads to apoptosis and defects in cognition and memory [6]. Not surprisingly, other neurotransmitters like GABA, histamine, and serotonin also have role in AD [7]. Of the various factors involved in causing AD like apolipoprotein genotype, mitochondrial defects, insulin dependent diabetes, environmental factors and diet; ageing is the major one [2].

Parkinson's disease (PD) is the second most common neurodegenerative disorder which is associated with motor dysfunction but its etiology is unknown. It affects approximately 1% of population aged 65–69 and

***Corresponding author:**
Shikha Girdhar
Department of Pharmacology, JCDM College of Pharmacy, Sirsa-125055, India
Email: rahejashikha[at]gmail.com

the prevalence increases to 3% in the 80-year-old or above group [8]. PD is clinically diagnosed by the presence of bradykinesia, postural instability, tremor and rigidity. Its neuropathological features include selective degeneration of pigmented, dopaminergic neurons in the pars compacta of the substantia nigra (Figure I), which is a cumulative effect of glutathione depletion, iron deposition, increased lipid peroxidation, oxidative DNA damage, mitochondrial dysfunction, excitotoxicity and alterations in anti-oxidant enzymes activities [9]. Other pathological observation in PD is the presence of intracytoplasmic proteinaceous inclusions called Lewy bodies which are the aggregates of α-synuclein [10].

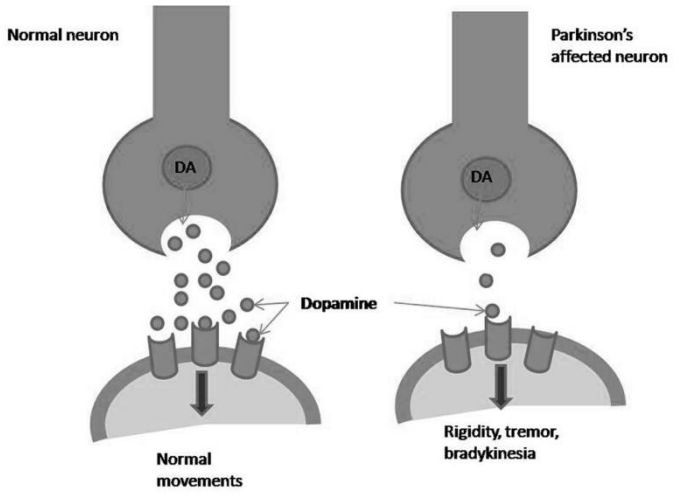

Figure 1: Brain regions affected by PD

Although, several pharmacologic treatments are available, still these neurodegenerative diseases remain incurable as all the current treatment options mainly ameliorate the symptoms by enhancing the neurotransmitter level or by inhibiting their metabolism to restore their imbalance [11]. Thus, there is a need to alter the underlying disease process by understanding the pathophysiology of these neurodegenerative disorders. Prevention may represent an ideal solution to the challenge posed by these conditions. Based on this, a number of disease modifying and preventive strategies are under investigation and herbal remedies are one of them [12]. The disease progression of AD and PD and different drug targets are shown in Figure II.

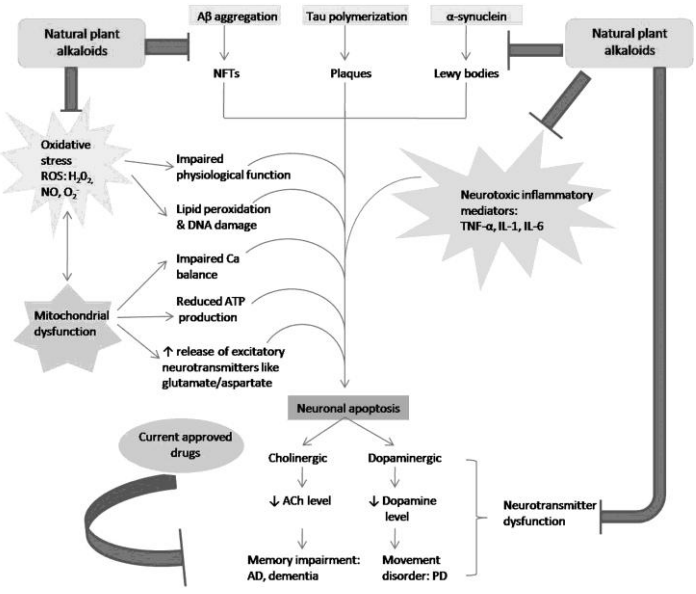

Figure 2: Neurodegenerative disease progression and multiple target sites for alkaloids

Nature is a rich source of medicinal plants having diverse phytochemical constituents like flavonoids, alkaloids etc. Many plants are being used world-wide in traditional medicinal remedies for various disorders from the ancient times. Out of the four FDA approved drugs for AD, galanthamine and rivastigmine are plant based drugs. Apart from these, there are several alkaloids which have shown potential to treat neurodegenerative diseases in preclinical studies owing to their multiple activities, such as neurotransmitter modulatory, anti-amyloid, anti-oxidant, and anti-inflammatory activities [13]. The aim of this review is to provide an overview of development of selected plant-derived alkaloids and their derivatives in the treatment of neurodegenerative diseases.

Current therapeutic strategies for treatment of Alzheimer's and Parkinson's diseases

The symptoms of AD can be directly correlated with the decreased cholinergic neurotransmission; therefore first and foremost approach is to increase the availability of ACh by inhibiting its degradation by the enzyme AChE. Based on this intervention, four AChE inhibitors were developed and approved by U.S. FDA. These include donepezil (Aricept®), rivastigmine (Exelon®), tacrine (Cognex®) and galanthamine (Razadyne®) are most commonly used for mild to moderate cases of AD [14]. However, tacrine is no longer marketed because of its poor tolerability and signs of hepatotoxicity in controlled trials [15]. The second promising approach is the anti-glutamatergic strategy based on which N-methyl D-aspartate (NMDA) receptor antagonist, memantine has been developed. It reduces the glutamate excitotoxicity and has shown beneficial effects in moderate to severe cases of AD [16]. Recently the focus is on disease modifying approaches like anti-amyloid, anti-tau, anti-inflammatory, caspase inhibitors and statins etc. which can delay the disease progression.

In case of PD, there is degeneration of the dopaminergic neurons resulting in diminished dopamine levels in brain and the most common therapeutic approach is to raise the levels of dopamine in brain, for which levodopa, the dopamine precursor, is most effective symptomatic treatment [13]. However, the chronic use of levodopa is associated with dyskinesias. Monoamine oxidase B (MAO-B) inhibitors, catechol-*o*-methyl transferase (COMT) inhibitors and dopamine agonists are the other available treatments of PD as these drugs either boost the levels of dopamine in brain or mimic the effects of dopamine. But the serious adverse effects associated with these drugs led to the development of novel non-dopaminergic treatments like adenosine receptor antagonists, NMDA antagonists, calcium channel blockers, glucagon like peptide-1 agonists, iron chelators, anti-inflammatory agents, anti-oxidants and gene therapy [17]. The various treatment strategies for AD and PD are mentioned in Table 1.

Herbal approach in the treatment of neurodegenerative diseases

Natural resources, specifically herbs are being widely used to treat pathological conditions of the CNS from the ancient times. There is a tradition to use different parts of the plants for the treatment of large number of diseases in many countries like China, Korea, Japan and India [13]. It has been predicted that the present global market of USD 60 billion for herbal product will grow to more than USD 5 trillion by the year 2020 [18]. Although quality control and safety are major issues in the use of herbal medicine, huge number of population still rely on the herbal medicine because they are cheap and have less side effects as compared to the modern synthetic medicine. Though difficulty is posed due to complex pathology of neurodegenerative diseases and multiple pathological aspects of herbal drugs, yet the development of herbal drugs for the treatment of neurodegenerative diseases is at new horizon. However, understanding the biological mechanism of herbs remains the important part of herbal research [2].

Table 1: Current treatment strategies of AD and PD

Strategy	AD	PD
Neurotransmitter modulation (approved therapies)	AChE Inhibitors NMDA antagonist	Dopamine precursor MAO-B inhibitors COMT inhibitors Dopaminergic agonists Anti-cholinergics
Disease modifying therapies (under investigation)	Amyloid based therapy	α-Synuclein based therapy
	• Modulation of secretase • Prevention of amyloid aggregation • Promoting amyloid clearance	• Prevention of α-synuclein aggregation • Blockade of α-synuclein fibril formation • Modulation of α-synuclein related lipidome
	Tau based therapy	Non-dopaminergic therapy
	• Inhibition of Tau hyperphosphorylation • Degradation of Tau • Inhibition of Tau oligomerization	• Adenosine receptor antagonists • NMDA antagonists • Glucagon like peptide-1 agonists
Immunotherapy	• Passive immunization Solanezumab Crenezumab • Active immunization CAD106	• Passive immunization Solanezumab • Active immunization PD01A
Gene based therapy	Modulation of expression of presenilin	Modulation of expression of synapsin 3
Other	Oxidative stress reduction Anti-inflammatory agents Caspase inhibitors Metal chelators Statins PPAR-γ	Anti-inflammatory agents Melatonin Nicotine Calcium channel blockers Anti-oxidants Iron chelators

PPAR-γ: Peroxisome proliferator-activated receptor-γ

Different mechanistic approaches of alkaloids in Alzheimer's disease

Alkaloids as AChE inhibitors

AChE is the enzyme responsible for degradation of ACh. AChE inhibitors replenish the levels of ACh in the hippocampal and cortical areas of brain as cholinergic deficit is identified in these areas in AD. The AChE inhibitory activity of alkaloids is thought to be due to positively charged nitrogen moiety which binds to anionic aspartate residue and a region separated by lipophillic area from positive charge, which can form a hydrogen bond with tyrosine or serine residue, but this does not explain the binding characteristics of other natural products with AChE inhibitory activity [19]. As most of the synthetic drugs used for AD are AChE inhibitors, extensive search has been carried out in past few years to find out the potential AChE inhibitors from plant sources. Like galanthamine, many plant alkaloids have AChE inhibitory activity and are discussed elsewhere [20, 21]. The different alkaloids effective in AD and PD and their current status are shown in Table 2.

Table 1: Major alkaloids effective in AD and PD

Alkaloid	Class	Source	Family	Mechanism	Disease	Stage of development	Ref.
Arecoline	Pyridine	*Areca catechu*	Arecaceae	Muscarinic receptor agonist	AD	preclinical	[20]
Acetylcorynoline	-	*Corydalis bungeana*	Papaveraceae	Inhibitor of α-synuclein aggregation	PD	preclinical	[93]
Berberine	Isoquinoline alkaloid	*Coptis chinensis*	Rananculaceae	AChEI, BChEI, anti-oxidant, MAO inhibitor, anti-amyloid	AD	preclinical	[53]
Caffeine	Xanthine	*Coffea arabica*	Rubiaceae	Reduces Aβ formation, adenosine receptor antagonist	AD, PD	phase II	[71, 72]
Dehydroevodiamine	Indole	*Evodia rutaecarpa*	Rutaceae	AChEI	AD	preclinical	[20]
Epiberberine	Benzyl-isoquinoline	*Corydalis species*	Papaveraceae	AChEI	AD	preclinical	[101]
Galanthamine	Isoquinoline	*Galanthus woronovii*	Amaryllidaceae	AChEI, allostearic modulation of	AD	FDA approved	[40]

		Galanthus nivalis		nicotinic ACh receptor			
Geissospermine	Indole	*Geissospermum vellosii;*	Apocynaceae	AChEI	AD	preclinical	[21]
Groenlandicine	Isoquinoline	*Coptis chinensis*	Ranunculaceae	AChEI, BACE1 inhibition, anti-oxidant	AD	preclinical	[101]
Jateorrhizine	Isoquinoline	*Coptis chinensis*	Ranunculaceae	AChEI, BACE1 inhibition, anti-oxidant	AD	preclinical	[101]
Harmaline	Indole β-carboline	*Peganum harmala*	Nitrariaceae	COMT inhibitor, AChEI	PD, AD	preclinical	[82]
Huperzine A	Lycopodium alkaloid	*Huperzia serrata*	Huperziaceae	AChEI, anti-oxidant, inhibits NMDA and glutamate toxicity	AD	clinically approved in China	[51, 102]
Ibogaine	Indole	*Tabernanthe iboga*	Apocynaceae	Dopaminergic agonist, NMDA antagonism	PD	preclinical	[78]
Isorhynchophylline	Indole	*Uncaria tomentosa*	Rubiaceae	Anti-amyloid, degradation of α-synuclein	AD, PD	preclinical	[75, 76]
Lobeline	Piperidine	*Lobelia inflata*	Camapnulaceae	Nicotinic agonist	AD	preclinical	[20]
Lycojapodine A	Lycopodium	*Lycopodium japonicum;*	Lycopodiaceae	AChEI	AD	preclinical	[101]
Lycorine	Isoquinoline	*Narcissus pseudonarcissis*	Amaryllidaceae	AChEI	AD	preclinical	[101]
Nigellastrine	β-carboline	*Peganum nigellastrum*	Zygophyllaceae	AChEI	AD	preclinical	[21]
Nicotine	Pyridine	*Nicotiana tabacum*	Solonaceae	Nicotinic agonist, anti-amyloid	AD, PD	phase III, IV	[67, 69]
Piperine	Piperidine	*Piper nigrum*	Piperaceae	MAO inhibitor	PD	preclinical	[86]
Physostigmine	Pyrroloindole	*Physostigma venosum*	Leguminosae	AChEI	AD	clinical trials discontinued	[32]
Pseudoberberine	Benzyl-Isoquinoline	*Corydalis species*	Papaveraceae	AChEI	AD	preclinical	[101]
Pseudocoptisine	Benzyl-isoquinoline	*Corydalis species*	Papaveraceae	AChEI	AD	preclinical	[101]
Psychollatine	Indole	*Psychotria umbellate*	Rubiaceae	MAO inhibitor	PD	preclinical	[84]
Rutaecarpine	Indole	*Evodia rutaecarpa*	Rutaceae	AChEI	AD	preclinical	[20]
Salsoline	Isoquinoline	*Salsola oppositofolia*	Chinopodiaceae	AChEI	AD	preclinical	[21]
Salsolidine	Isoquinoline	*Salsola oppositofolia*	Chinopodiaceae	AChEI	AD	preclinical	[21]
Sinapine	Sinapic acid choline ester	*Raphanus sativus*	Brassicaceae	AChEI	AD	preclinical	[21]
Uleine	Indole	*Himatanthus lancifolius*	Apocynaceae	AChEI	AD	preclinical	[101]

AChEI: acetylcholineestrase inhibitor; BACE1: β-secretase

Alkaloids as anti-oxidants

It has been widely established that oxidative stress plays an important role in pathophysiology of neurodegeneration. The major pathological changes involved in AD and PD are accumulation of free radicals, oxidative damage to neuronal cells and diminished cellular anti-oxidant pool [22]. Therefore natural antioxidants have important role in such diseases as they can reduce the oxidative stress. A plenty of natural compounds with antioxidant potential are being investigated for treatment of AD and PD. The anti-oxidant activities of various alkaloids like berberine and huperzine A have been widely demonstrated [23, 24] and also discussed in further sections.

Alkaloids as anti-amyloid agents

Amyloid cascade theory states that there is an increased production or decreased clearance of amyloid in AD. As mentioned previously amyloid plaques are formed in AD due to the accumulation of Aβ42 which is followed by aggregation, oligomerization, and fibril and proto-fibril formation. Abnormal processing of APP is responsible for this deposition. The two enzymes, β-secretase and γ-secretase which catalyze the cleavage of amyloid-β peptide are important targets in treatment of AD [5]. Until recently, these approaches were not explored but recent studies have shown that anti-amyloid strategy can be a powerful approach in halting the progression of AD [25]. Berberine has gained attention in this direction as it can ameliorate amyloid-β pathology in AD [26]. *In vitro* studies have shown that nicotine can

prevent the precipitation of β-(1-42) peptide as amyloid like deposit [27].

Alkaloids as NMDA antagonists

It has been confirmed that NMDA induced neurotoxicity and glutamate induced excitotoxicity have a role in neurodegenerative diseases. Overactivity of NMDA receptors results in production of free radicals which are responsible for neuronal damage and cell death [28]. Therefore, inhibition of NMDA and glutamate toxicity is powerful therapeutic approach for neurodegenerative diseases. Studies have shown that the plant alkaloids like huperzine A and ibogaine have inhibitory effect against NMDA and glutamate toxicity [29, 30].

Potential alkaloids for Alzheimer's disease

Physostigmine

The first alkaloid of natural origin which was investigated as AChE inhibitor was physostigmine, isolated from calabar bean, the seeds of *Physostigma venosum* balf. (leguminosae). Physostigmine protected mice against cognitive impairment and improved learning in rats [31]. It has also shown to improve cognitive function both in normal and AD patients [19]. But its clinical efficacy was questioned because of its shorter half life, narrow therapeutic index and peripheral side effects. Physostigmine also inhibits another enzyme called butylcholinestrase (BChE) which also has important role in etiology of AD. BChE inhibition may be responsible for some of the side effects of physostigmine like nausea, vomiting, dizziness, headache and diarrhea [32]. Numerous synthetic analogues of physostigmine having better pharmacokinetic profile and lesser side effects have been prepared. Of particular therapeutic relevance is rivastigmine, which is being clinically used for mild to moderate cases of AD. Other important derivatives of physostigmine having AChE inhibitory activity are phenserine, tolserine and genserine. Phenserine has been found to enhance cognition in animal models as well as AD patients by dual mechanism i.e. AChE inhibition and anti-amyloid activity. After showing good tolerability in phase II trials, phenserine underwent evaluation in phase III ranomised, placebo controlled, double blind trials designed to assess its safety and ability to lower the levels of β-amyloid in plasma but the results were disappointing and it failed in these trials [33]. Its (+)-enantiomer (Posiphen) has been investigated in Phase 1 trials by QR Pharma. Bisnorcymserine, a BChE inhibitor and another follow-on compound of phenserine is being investigated for AD in Phase I by National institute of ageing (www.clinicaltrials.gov). Interestingly, phenserine and posiphen also showed their potential for PD by lowering α-synuclein expression in neural cell lines in one of the study [34]. Ganstigmine (CHF-2819), a genserine derivative reverses the scopolamine induced memory deficit in rats [35] and protects against Aβ neurotoxicity in chicken cortical neurons [36]. It was clinically tested in phase II by Chiesi Farmaceutici for treatment of AD however; the company discontinued the development of drug in order to focus resources on other therapeutic areas [37]. The different derivatives of physostigmine and their clinical status are shown in Table 3.

Table 3: Alkaloid derivatives under investigation for AD and PD

Alkaloid	Derivative	Disease	Company	Status	Refs.
Physostigmine	Rivastigmine	AD	Novartis	Approved for mild to moderate cases of AD	[7]
				Failed in phase III	
	Phenserine	AD, PD	QR Pharma	Phase I	[33]
	Posiphen	AD, PD	QR Pharma	Phase I	[103]
	Bisnorcymserine	AD	National Institute of Ageing		[104]
			Chiesi Farmaceutici	Discontinued	
	Ganstigmine	AD			[37]
Galanthamine	Memogain	AD	Neurodyn Inc.	Phase I	[105]
Anabaseine	GTS-21	AD	CoMentis	Phase II	[106]
Huperzine A	ZT-1	AD	Debiopharm International	Phase II	[107]
Caffeine	Istradefylline (KW-6002)	PD	Kyowa Hakko Kirin Pharma Inc.	Phase III	[108]

Galanthamine

Galanthamine is a reversible and selective AChE inhibitor isolated from *Galanthus woronovii*, *Galanthus nivalis* L., some species of *Narcissus* and *Leucojum aestivum*.

Several preclinical studies were carried out to determine the pharmacological activity of galanthamine. In one of the study, swim-maze test was utilized to access the special memory performance in NBM- lesioned mice and it was found that the administration of galanthamine improved their performance [38]. In another study, it was found that galanthamine reduced the scopolamine induced learning and memory deficit in a significant manner [39]. It influences the central cholinergic pathway by dual mechanism, *i.e.,* first by inhibiting AChE, it increases the ability of ACh in synaptic cleft and secondly the allosteric modulation of nicotinic Ach receptor by which it potentiates the nicotinic neurotransmission [40].

After evaluating the effectiveness of galanthamine in preclinical studies for AD, a large number of clinical investigations were carried out to see its beneficial effects in the diseased patients. All the clinical trials were randomized double blind, placebo control and multi-centered. A minimental state examination score of 11-24 [41] and AD assessment scale; ADAS-cog [42] were the criteria to diagnose mild to moderate dementia. From the clinical trials, it was predicted that this alkaloid was specifically effective in patients with mild AD. It (24 mg/d) improved the cognition in patients with mild AD as indicated by the data obtained from the four randomized clinical trials and there were no signs of hepatotoxicity [43]. After the successful clinical trials, it was first launched in market as "NIVALIN" in 1996 by Sanochemia Pharmazeutika of Austria for treatment of AD, and later as "REMINYL" in many countries such as Argentina, Australia, Belgium, Canada, Denmark, France, Germany, Greece, Italy, U.S. etc. from 2000 to 2003 [40]. Nowadays, galanthamine is marketed under the name "Razadyne". A number of synthetic analogues of galanthamine have been prepared however their clinical usefulness has not yet been explored. Memogain® (Gln-1062), a prodrug of galanthamine has shown to improve cognitive effects in animal models of amnesia and bioavailability in brain as compared to galanthamine with few adverse effects [44]. It is being evaluated in initial phase IA clinical trials in Netherlands by Neurodyn Inc. for AD (www.drugs.com). The

development of galanthamine as AChE inhibitor led to the search for other alkaloids having AChE inhibiting property. A lycopodium alkaloid, huperzine A is another good example in this continuum, which has shown promising results, clinically, in treatment of AD [45].

Huperzine A

Huperzine A is extracted from Chinese herb *Huperzia serrata* commonly known as club moss. It has neuroprotective and anti-oxidant property and its formulation Qian Ceng Ta has been used to treat memory loss [46]. It is reversible AChE inhibitor and increases the amount of ACh in synaptic cleft and thereby improves cholinergic neuronal transmission. Also, compared to synthetic drugs it has longer duration of action, high therapeutic index and minimal peripheral cholinergic side effects.

Preclinical studies

It was revealed in different animal studies that huperzine A attenuated cognitive deficits in various tasks including spatial radial arm maze discrimination, water maze and passive footshock avoidance [47]. It was also observed that huperzine A was more effective than other AChE inhibitors like galanthamine and tacrine [48]. *In vitro* studies revealed that in hippocampal neuronal cells, cortex and synaptic plasma membranes, it also inhibited NMDA toxicity. Huperzine A also decreased neuronal cell death caused by glutamate toxicity in cell culture studies which demonstrated its neuroprotective effect [12, 30].

A large number of clinical studies were conducted in China to see the beneficial effects of huperzine A in AD patients. In one of the AD clinical studies, huperzine A was administered (30μg, i.m.) in a group of 100 patients with Alzheimer's and other memory problems and it was compared with dihydroergotoxine (6mg). The results revealed that huperzine A had a positive effect on the memory as compared to dihydroergotoxine and with no remarkable side effects [49]. In another multicenter, randomized, double blind, placebo controlled trial, huperzine A (0.05 mg, i.m.) or placebo twice daily for 1 month was given in 56 patients with multi-infarct dementia or AD and there was significant improvement in Memory Quotient of the patients when measured with Wechsler Memory Scale [50]. Further, huperzine A significantly improved the cognitive, non cognitive and activities of daily living functions in AD patients when administered 300 μg/day for first 2-3 weeks and then 400 μg/day for the next 4-12 weeks [51]. Safety of huperzine A was also determined in clinical studies and all the trials reported very mild side effects like nausea, vomiting, diarrhoea and dizziness. After China, clinical trials of huperzine A on AD patients also started in other countries. In U.S., phase II clinical trial of huperzine A has been conducted by National Institute of Aging and Alzheimer's disease co-operative study (http://www.ClinicalTrials.gov). The derivative of huperzine A, ZT-1 has also been evaluated for its safety and efficacy in a recent phase II study. It has been found that repeated monthly s.c. injection of sustained release implant of ZT-1 is safe in patients with moderate AD (www.clinical trials.gov/NCT00423228).

Berberine

Berberine is a natural alkaloid possessing isoquinoline ring isolated from *Coptis chinensis*, a Chinese herb. It has diverse pharmacological properties like anti-inflammatory, anti-hypertensive, anti-oxidant, anti-depressant, anti-cancer, anti-microbial, anti-diarrhoeal and lowering cholesterol and glucose etc. [52], and is a promising drug for diabetes, coronary artery disease, hyperlipemia and ischemic stroke etc. Owing to the multiple anti-oxidant; AChE, BChE and MAO inhibitory properties and Aβ level reducing activities, berberine has the potential to treat AD.

Feiqi Zhu and Caiyun Qian investigated the effect of berberine chloride on the spatial memory in the rat model of AD and it was demonstrated that berberine chloride (50 mg/kg) once daily for 14 days significantly ameliorated the spatial memory impairment in rats when tested by Morris water maze model [53]. Berberine also possesses anti-oxidant activity. It was revealed in a study that berberine could scavange the reactive oxygen species and reactive nitrogen species like peroxynitrites which are involved in Aβ formation and accumulation. It has also been reported to exhibit inhibitory activity against AChE and BChE as both are involved in pathogenesis and progression of AD. It inhibited AChE and BChE at IC_{50} of 0.44μM and 344μM respectively [54]. Interestingly, berberine also possesses MAO inhibitory activity. Apart from PD, MAO-B inhibitors also have neuroprotective effect in AD [55]. It is evident from the reports that berberine inhibits both MAO-A and MAO-B with a value of 126 μM and 90 μM respectively [56]. Additionally, berberine can also reduce Aβ levels by altering APP processing in human neuroglioma H4 cells at the concentration range of 0.1 - 100 μM without cellular toxicity [57].

Clinical investigations have been carried out to test the efficacy of berberine in treatment of Type 2 diabetes mellitus, oriental sore, diarrhea, trachoma, hypercholesterolemia and congestive heart failure [52], but the clinical efficacy of berberine in the treatment of AD still has to be established.

Nicotine

Nicotine is a pyrrolidine alkaloid found in *Nicotiana tobaccum* and constitutes approximately 0.6 to 3.0% of dry weight of tobacco. Studies have demonstrated a connection between smoking and lower incidence of AD and PD [58]. Nicotinic acetylcholine receptors have significant role in pathogenesis of AD as these receptors are found in hippocampus, amygdala and frontal cortex, the brain areas involved in memory function [59]. Chronic treatment with nicotine resulted in upregulation of nicotinic ACh receptors in several areas of brain [60].

Salomon *et al*. Y reported that *in vitro* nicotine inhibits amyloid formation by β-peptide by binding to the more soluble α-helical structure, which inhibits the conversion of α-helix to β-sheet during amyloidosis [27]. Cotinine, the major metabolite of nicotine, also reduces amyloid formation and inhibits Aβ42 aggregation. In addition to cholinergic system, NPYergic (NPY: neuropeptide) system also plays an important role in mediating nicotine induced improvement in learning and memory as NPY receptors are also present in hippocampus and amygdala. Recently, it has been shown that nicotine evokes improvement in learning and memory mediated through $NPYY_1$ receptors in AD like condition induced by colchicines in rats [61]. In this study the cognitive functions were assessed by Morris water maze task and on acute nicotinic administration (0.1-0.5mg/kg, i.p.), dose dependent improvement in learning and memory in colchicines treated rats was observed. Nicotine decreased escape latency and increased the time spent in target quadrant as compared to the saline treated rats.

Various clinical studies have shown that nicotine treatment to AD patients improves attention and memory. Newhouse and co-workers in 1988 demonstrated that i.v. administration of nicotine to AD patients improved the cognitive functioning [62]. Effect of acute s.c. nicotine on attention, information processing and short term memory was studied and improved attention related performance in AD was reported [63]. In another study, nicotine skin patch treatment for two weeks significantly improved cognitive functions in AD patients [64]. White and Levin studied the effect of transdermal nicotine in AD in a four week trial and they found the significant improvement in attentional performance measured by continuous performance task [65].

In addition, the effect of nicotine has also been studied on mild cognitive impairment as there is evidence that people with mild cognitive impairment are at high risk for developing dementia [66]. White and Levin carried out a double blind placebo control cross over

trial in ten subjects with mild cognitive impairment. In this study, nicotine patch application for 16 hours a day significantly improved ratings of overall performance [67]. Further, the effect of nicotine in subjects treated with cholinesterase inhibitor, tacrine was studied and results showed improvement in sensory detection, attention and processing [68]. In addition to AD, the beneficial effects of nicotine were also studied in PD patients. Acute and chronic nicotine administration improved the cognitive and motor performance in the patients of PD [69].

Caffeine

Caffeine is a psychoactive xanthine alkaloid commonly found in coffee, tea, soft drinks and chocolate. Epidemiologic studies have suggested that caffeine intake is inversely related to cognitive impairment in AD and PD [70, 71]. Further, various controlled studies were carried out to evaluate the protective effect of caffeine against cognitive impairment in AD. A preclinical study has shown that long-term caffeine reduces Aβ formation in transgenic (APPsw) mice as well as aged mice by reducing the expression of presenilin 1 and β-secretase (BACE1) [72]. Caffeine is adenosine receptor antagonist and has been found to reverse the neurotoxicity in experimental models of AD and PD [73]. The central effects of caffeine are thought to be mediated primarily through the blockade of A_1 and A_{2A} receptors out of four adenosine receptors A_1, A_{2A}, A_{2B}, and A_3. Administration of caffeine and SCH58261, a selective A_{2A} receptor antagonist showed protective effect against cognitive impairment and oxidative stress [74].

Isorhynchophylline

Isorhynchophylline, an alkaloid obtained from *Uncaria* species has extensive therapeutic potential for cardiovascular and CNS diseases including hypertension, bradycardia, dementia and amnesia. Mohamed et al. investigated the effects of *Uncaria tomentosa* total alkaloid and its oxindole alkaloid components, uncarine E, uncarine C, mitraphylline, rhynchophylline and isorhynchophylline on the impairment of retention performance using a step down passive avoidance test in mice. The amnesic and test drugs were given to animals before training and retention performance was assessed 24 h after training and it was observed that *Uncaria tomentosa* total alkaloid (10-20 mg/kg, i.p.) and the alkaloid components (10-40 mg/kg, i.p.) as well as the muscarinic receptor agonist oxotremorine (0.01 mg/kg, i.p.) significantly attenuated the deficit in retention performance induced by scopolamine, a muscarinic receptor antagonist (3 mg/kg, i.p.) [75]. It has also been reported to have the neuroprotective effect against β-amyloid induced neurotoxicity [76].

Different mechanistic approaches alkaloids in Parkinson's disease

In PD there is degeneration of dopaminergic neurons in brain resulting in diminished levels of dopamine, leading to rigidity, tremor and hypokinesia. Thus, different approaches for treatment of PD focus on the elevation of dopamine levels either by the inhibition of MAO-B or COMT which metabolize dopamine to less active compounds or by administering dopaminergic agonists and dopamine precursors.

Alkaloids as dopamine precursor

Dopamine itself cannot cross the blood brain barrier; therefore its prodrug L-DOPA is given which is converted to dopamine in brain. L-DOPA, a precursor of dopamine can be obtained from various species of bean; especially *Mucuna* sp. In Ayurveda, powdered seeds of *Mucuna* sp. have been used for nervous system disorders [20]. However, the drug can also be synthesized now.

Alkaloids as dopaminergic agonists

Apomorphine, a derivative of opium alkaloids is dopaminergic agonist at D1 and D2 receptors. Salsolinol, found in seeds of *Theobroma cacao* L. (sterculiaceae) has also shown dopaminergic activity at D2 receptors and neuroprotective effect [77]. Further, Ibogaine, an alkaloid obtained from *Tabernanthe iboga* Baill (apocynaceae) has shown to release dopamine from striatal cells [78]. It also acts as NMDA receptor antagonist and inhibits the NMDA induced excitotoxicity [29]. Tropane alkaloid, scopolamine has shown to increase dopaminergic activity and has been used to treat PD. It also antagonizes cholinergic activity at muscarinic receptors [79].

Alkaloids as COMT inhibitors

Most of the phytochemicals having anti-oxidant and neuroprotective properties have catechol ring in their structurers [80]. COMT deactivates the biologically active catecholamines like dopamine and epinephrine and thus, it plays an important role in Parkinsonism as there is progressive loss of dopaminergic neurons in PD. Thus, COMT inhibitors can increase the dopamine level by preventing its deactivation. Several natural compounds are being investigated for COMT inhibiting property like tea catechins have great inhibitory potency against COMT [81]. In one of the study, COMT inhibiting effect of natural compounds extracted from the leaves of *Cistus parviflorus* and *Vitex agnus-castus*, and seeds of *Peganum harmala,* was observed. It was found that alkaloid extract obtained from *P. harmala* seeds containing β-carbolines like harmaline, harmine, harmalol, vesicinone, vasicine etc. had the highest COMT inhibitory effect among the different plant extracts. The major alkaloid in *P. harmala* seed extract, harmaline was found to be responsible for the observed inhibitory effect [82].

Alkaloids as MAO inhibitors

Other targets in PD are MAOs which are of two types MAO-A and MAO-B. MAOs are responsible for oxidative deamination of monoamines like 5-hydroxy tryptamine, histamine, catecholamines (dopamine, noradrenaline and adrenaline) as well as xenobiotic amines such as tyramine, phenylethylamines etc. MAO-B mainly deaminate dopamine therefore the selective MAO-B inhibitors like rasagiline, l-deprenyl are clinically used for treatment of PD as they increase the brain dopamine level [83]. It has been recently demonstrated that the alkaloids from different psychotria species have the inhibitory effect on AChE, BChE and MAO-A and B. The major alkaloid psychollatine, found in *Psychotria umbellate* leaves exhibits analgesic, anxiolytic, anti-depressants and amnesic effect in different animal models. Alkaloids obtained from *Psychotria suterella* and *Psychotria laciniata* have also shown the inhibitory effect on MAO-A and MAO-B in the rat brain [84].

Piperine, alkaloid obtained from black pepper plant *Piper nigrum,* inhibited both MAO-A and MAO-B in mice brain. The study indicated that piperine can competitively inhibit MAO-A (IC_{50} value: 20.9 µm) and MAO-B (IC_{50} value: 7.0 µm). Lineweaver Burk plot indicated that K*i* values for MAO-A and MAO-B inhibition are 19±0.9 µm and 3.19± 0.5 µm respectively. It was implicated that piperine possesses potent anti-depressant property and thus could have potential in PD [85]. Further, MAO-A and MAO-B inhibitory activity of piperine derivatives has also been evaluated *in vitro* by the use of Z-factor analysis and it was found that most of the compounds were more selective for MAO-B as compared to MAO-A, which again suggested that piperine may have a beneficial role in PD [86].

Alkaloids as adenosine receptor antagonists

Adenosine A_{2A} receptors are one of the novel targets for the treatment of PD. Recently it has been suggested that adenosine blockade can be a disease modifying strategy for PD also [73]. Caffeine prevents the loss of dopaminergic neurons and delays neuronal degeneration in rats when

administered after one week of start of disease [87]. It has been found that 8-(3-chlorostryryl caffeine, a selective A_{2A} receptor antagonist inhibits the levodopa induced motor impairment in 6-hydroxy dopamine (OHDA)-lesioned rats through a downstream DARPP-32 and ERK1/2 signaling pathway [88]. A recent open label dose response phase II study has been conducted to determine the efficacy of caffeine for motor manifestations of PD (www.clinicaltrials.gov/NCT01190735)

Istradefylline (KW-6002), a caffeine analog and selective adenosine receptor antagonist, has shown to improve motor disability in neurotoxin induced experimental models in rodents and monkeys [89]. Its safety and efficacy was evaluated in a 12 week, double blind study which demonstrated that it was safe and well tolerated as monotherapy in PD patients [90]. Administration of istradefylline and levodopa in PD patients caused reduction in "of" time and increase in "on" time without causing dyskinesia [91].

Alkaloids as inhibitors of α-synuclein aggregation

Accumulation of α-synuclein results in formation of lewy bodies which is key feature of PD. Isorhynchophylline**,** apart from showing protective effect against amyloid induced toxicity, also promotes the degradation of α-synuclein and protects the neuronal cells via autophagy-lysosome pathway [92]. Very recently, acetylcorynoline, an alkaloid derived from corydalis bungeana has shown to decrease the degeneration of dopaminergic neurons and prevention of α-synuclein aggregation in animal models of PD [93-100].

CONCLUSION

The available drugs for AD and PD till date focus on the symptomatic improvement but do not modify the disease progression and also have numerous adverse effects. One of the four approved AChE inhibitors for AD, tacrine is no longer marketed due to its poor tolerability and hepatotoxicity as shown in clinical studies. Numerous disease modifying strategies have been explored in the recent years and many compounds are being investigated under these strategies but none of them have successfully reached the market. In this context, plant based drugs have also emerged as a novel insight. Apart from targeting the neurotransmitter abnormalities, natural alkaloids also have anti-amyloid, anti-oxidant and anti-inflammatory properties. Thus, natural alkaloids have a multimechanistic approach in treatment of neurodegenerative diseases. Further clinical studies suggest that natural alkaloids are safe as compared to the synthetic drugs. There is evidence that huperzine A is safe and effective for AD and age related memory impairment, but further long term observation and clinical comparison with other AChE inhibitors is needed. There are several alkaloids and derivatives which have tremendous scope in treatment of neurodegenerative diseases. But only one or two of them have widespread clinical use. Few of them are in different phases of clinical investigation, yet there are many more alkaloids which have not entered clinical trials. There is an urgent need to design clinical trials for such compounds. Further, more emphasis should be given on minimizing the methodological errors in order to control the failures in clinical trials. Disappointingly, phenserine failed in phase III clinical trials after being investigated for several years. Some of the alkaloids have been dropped from clinical trials due to lack of efficacy or serious adverse effects. Although successes in translating the outcome of preclinical studies to clinical trials are very limited, still natural alkaloids are promising hope in slowing the progression of neurodegenerative diseases.

CONFLICT OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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