Chapter

Alkaloids as New Leads for Neurodegenerative Diseases

Farah Al-Mamoori and Ashraf M.A. Qasem

Abstract

Conventionally, diseases involving the selective loss of neurons are referred to as neurodegenerative diseases. Traditional and more recent compounds have been explored, but they only provide symptomatic benefits and have a large number of negative effects. It will be regarded as a modern vision if stronger molecules are found that can stop the pathophysiology of these diseases. In order to replace existing medications, natural compounds are being developed from plants and other sources. Natural products, including alkaloids that originate from plants, have emerged as potential protective agents against neurodegenerative disorders (e.g., Alzheimer's and Parkinson's), psychiatric conditions, and many more. They provided unique lead compounds for medicine. Alkaloids could be exploited as starting materials for novel drug synthesis or, to a lesser extent, used to manage neurodegenerative-related complications due to their diverse mechanistic effects. This chapter aims to highlight the importance of alkaloids as new leads for the development of potential clinical drug candidates for the management and treatment of neurodegenerative diseases.

Keywords: alkaloids, leads, neurodegenerative diseases, Parkinson's disease, Alzheimer's disease

1. Introduction

Neurodegenerative diseases are debilitating conditions that affect memory, cognition, mobility, and overall functioning. Although these diseases have diverse patterns of signs and symptoms, they have several characteristics: A high correlation with age, protein aggregation that is abnormal, and a natural history that is gradual and relentless. This group of illnesses is likewise distinguished by a slow beginning, with neuropathological alterations developing years before clinical manifestation [1]. Instances of neurodegenerative diseases include: Alzheimer's disease and Parkinson's disease.

Worldwide, dementia affects more than 25 million people, the majority of whom have Alzheimer's disease. It has had a significant influence on affected individuals, carers, and society in both developed and developing countries [2]. The abundance of experimental and clinical evidence suggests that Alzheimer's disease is a complicated disorder characterized by extensive neurodegeneration of the central nervous system with significant involvement of the cholinergic system, resulting in gradual cognitive

decline and dementia [3]. New approaches, such as the detection of amyloid-beta (Aβ) and tumor necrosis factors (NFTs), lead to the amyloid and tau theories as potential causes of Alzheimer's development. Multi-target compounds that inhibit cholinesterases while also interfering with Aβ- aggregation and/or tau protein neuroinflammation may be effective in the treatment of Alzheimer's disease. Natural compounds, particularly plant alkaloids, have been a steady supply of innovative choices for the treatment of Alzheimer's disease. For example, the prototype of rivastigmine, physostigmine (*Physostigma venenosum*), is an cholinesterase enzyme inhibitors (IChE) inhibitor and allosteric modulator of the central nicotinic receptor. Galanthamine (*Galanthus woronowii*) is a selective acetylcholinesterase inhibitor, an allosteric modulator of the central nicotinic receptor, an inhibitor of Aβ aggregation, and an inducer of hippocampus neurogenesis [4]. Alkaloids have been one of the most appealing classes for searching for novel medications since the release of the Amaryllidaceae alkaloid as a drug in 2001 [3].

Parkinson's disease is the neurodegenerative disease with the second-highest prevalence. The age-adjusted prevalence was 205.89 per 100,000 people. The prevalence of advanced Parkinson's disease increased with age, from 3.77% in the 40–49 year age group to 25.86% in those over 89 years [5]. The development of pharmacotherapy for Parkinson's disease in terms of historically significant plant-derived substances, *Atropa belladonna* (deadly nightshade), *Hyoscyamus niger* (henbane), and *Datura stramonium* (thorn apple or jimsonweed), includes large amounts of pharmacologically potent anticholinergic tropane alkaloids (atropine, hyoscyamine, and hyoscine) [6].

Alkaloids, the main natural medicinal source, are a little-explored component of plant chemistry. They are cyclic organic compounds with at least one nitrogen atom [7]. The majority are biologically active. Alkaloids can be classified based on their ring chemistry or the amino acid from which they are formed [8]. The richness of alkaloid content varies between plant species, but most include a variety of these substances that are different in both their molecular structure and the biology of their effects. Individual plant alkaloid levels vary by component, life cycle, and season [9]. According to a review, 84% of medications licensed for central nervous system indications are derived from naturally occurring compounds [10].

Historically, the pharmaceutical industry originated from traditional plant medical knowledge. Natural scaffolds share molecular characteristics that can improve affinity with receptor binding sites. Natural structures confer more chirality (resulting in unique D- and L- stereoisomers) and more rigidity (due to ring conformations) than fully synthesized agents [10]. These chemicals can also go through the blood-brain barrier more easily. Because of evolutionary links between plants and mammals, natural products and natural-inspired medications may have a favorable influence on neurotransmitter systems [6]. This chapter summarizes the role of alkaloids in the management and treatment of neurodegenerative diseases and identifies them as lead compounds in the development of potential clinical drug candidates (**Table 1**).

2. Plant alkaloids as new leads for neurodegenerative diseases

2.1 Purine alkaloids: Theacrine

Some plants, like tea, coffee, chocolate, and mate, make purine alkaloids like caffeine, theobromine, theophylline, 7-methylxanthosine, and theacrine. The alkaloid theacrine is found in *Camellia kucha*, which is in the family Theaceae.

Class of alkaloids	Alkaloids	Plant source	Pharmacological activity	References
Purine alkaloid	Theacrine **(1)**	*Camellia kucha*	• In various animal models of Parkinson's disease, theacrine **(1)** has been shown to reverse dopaminergic cell loss and behavioral impairment –6-OHDA treated rats, and - 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) treated mice, and zebrafish. Theacrine **(1)** alleviates apoptosis caused by oxidative damage and mitochondrial dysfunction.	[11]
Isoquinoline alkaloid	Berberine **(2)** Avicine **(3)** Chelerythrine **(4)** Sanguinarine **(5)** Aromoline **(6)**	*Berberis spp.* *Coptis chinensis,* *Phellodendron amurense,* *Hydrastis Canadensis,* *Zanthoxylum rigidum,* *Macleaya cordata* *Berberis vulgaris*	• Berberine **(2)** drastically reduced the level of the NLRP3 inflammasome, including the levels of NLRP3, the PYD and CARD domain-containing protein, cleaved caspase 1, and mature interleukin 1 beta in 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease mice. • Avicine **(3)** alkaloid had the highest cholinesterase inhibition, being more active against AChE than BChE It is a promising natural chemical and multifunctional candidate, serving as a good starting point for the creation of new Alzheimer's disease treatments. • Chelerythrine **(4)** and sanguinarine **(5)** demonstrated effective cholinesterase activity inhibition. • Aromoline **(6)** revealed significant hBuChE inhibitory action.	[12] [12] [13] [14]
Indole alkaloid	Geissoschizoline **(8)** *Conophylline* **(9)**	*Geissospermum vellosii* *Ervatamia microphylla*	• Geissoschizoline **(8)** inhibited both hAChE and hBChE via a mixed-type mechanism. Molecular docking experiments revealed geissoschizoline interactions with the active and peripheral anionic sites of hAChE and hBChE, indicating a dual site inhibitor profile. Furthermore, geissoschizoline demonstrated anti-inflammatory activity by lowering microglial NO and TNF- release. • In cultured brain cells, conophylline **(9)** was discovered to trigger autophagy. Autophagy activation improved cellular models of Parkinson's and Huntington's illnesses. As a result, conophylline **(9)** may prove effective in the development of chemotherapy for metabolic and neurological illnesses.	[15] [16]

Class of alkaloids	Alkaloids	Plant source	Pharmacological activity	References
Quinazoline alkaloid	Vasicinone **(10)** Dehydroevodiamine **(11)**	*Adhatoda vasica Evodiae fructus*	• The findings showed that vasicinone **(10)** promoted neuroprotection in SH-SY5Y cells via increasing autophagy and PINK-1/Parkin-mediated mitophagy. • Dehydroevodiamine **(11)** has a clear protective effect on the central nervous system. In recent years, a large number of studies have dehydroevodiamine reported that has a preventive effect on Alzheimer's disease induced by various models, and it exhibits good blood-brain barrier permeability.	[17] [18]
Protoalkaloid	Capsaicin **(12)**	*Capsicum annuum*	• Capsaicin **(12)** was found to inhibit apoptosis in a cell model of 6-OHDA-induced Parkinson's disease through regulating Actg1 and Gsta2. • Capsaicin **(12)** sped up the maturation of disintegrin and metalloproteinase, which stopped A from forming and changed the processing of Amyloid precursor protein towards cleavage. Capsaicin **(12)** also helped with other Alzheimer's disease -related diseases such as tau hyperphosphorylation, neuroinflammation, and neurodegeneration.	[19] [20]
Carbazole alkaloids	Clauselansiumines A **(13)** and B **(14)**	*Clausena lansium*	• Geranylated carbazole alkaloids displayed remarkable neuroprotective effects, with EC_{50} values ranging from 0.48 ± 0.04 to 12.36 ± 0.16 M. These geranylated carbazole alkaloids could be extremely important to the discovery of new agents for the treatment and prevention of Parkinson's disease.	[21]
Aporphine alkaloids	Compounds **(14)** and **(15)**	*Artabotrys spinosus*	• Two of isolated alkaloid exhibited the highest activity towards BChE and AChE	[22]
Norditerpenoid alkaloids	Lappaconitine **(16)** 3-*O*-acetylaconitine **(17)** Crassicauline A **(18)** Methyllycaconitine **(19)**	*Aconitum spp. Delphinium spp.*	• Activation of VGSC (3-*O*-acetylaconitine and crassicauline A) • Inhibition of VGSC (Lappaconitine) • Inhibition of nAChRS (methyllycaconitine)	[23] [24] [25] [26]

Table 1.
Summarize classes of alkaloids, their source, and neurodegenerative diseases they target.

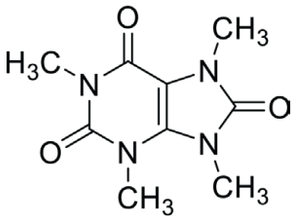

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Figure 1.
Theacrine (1).

The leaves of *C. kucha* contain both theacrine **(1)** and caffeine. Theacrine **(1)** is thought to be made from caffeine through an N-methyltransferase process that uses *S*-adenosyl-L-methionine (SAM) as a methyl donor. Theacrine **(1)** is an adenosine receptor blocker that speeds up movement and makes people feel less tired. In animal models of Parkinson's disease, theacrine **(1)** stops the loss of dopaminergic cells and changes in behavior by reducing oxidative damage and mitochondrial dysfunction (**Figure 1**) [11].

2.2 Isoquinoline alkaloids: Berberine, avicine, chelerythrine, sanguinarine, and aromoline

The isoquinoline alkaloids include, most famously, the opiates morphine and codeine, as well as berberine. Berberine **(2)** is an alkaloid found in the roots, rhizomes, stems, and bark of several medicinal plants, including *Berberis*, *Coptis chinensis*, *Phellodendron amurense*, and *Hydrastis canadensis*. Berberine significantly reduced nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3(NLRP3) inflammasome levels in Parkinson's disease mic [27].

Moreover, avicine **(3)** is an alkaloid isolated from *Zanthoxylum rigidum* (Rutaceae family). It is the most effective dual cholinesterase inhibitor, with IC_{50} values of 0.15 and 0.88 M for both AChE and BuChE, respectively [12]. Chelerythrine **(4)** and sanguinarine **(5)** are the main active ingredients of *Macleaya cordata* (Papaveraceae family) [28]. These bioactives inhibit cholinesterase activity extremely well [13]. Aromoline **(6)**, an isoquinoline alkaloid, was extracted from the root bark of *Berberis vulgaris* (Berberidaceae family), where it showed a significant inhibitory activity against human Butyrylcholinesterase (BuChE) with an IC_{50} = 0.82 ± 0.10 μM [14]. The therapeutic potentiality of aromoline **(6)** is worthy of further investigation, as the computational analysis supports its high affinity and selectivity for the active site of human BuChE (**Figure 2**).

2.3 Indole alkaloids: Geissoschizoline and conophylline

Indole alkaloids have been found in many well-known plant groups, such as Apocynaceae, Rubiaceae, Nyssaceae, and Loganiaceae. Researchers think that indole alkaloids may have brain effects because they have the same structure as endogenous amines and neurotransmitters. Several substances with an indole group have been shown to bind to different serotonin receptors[29, 30].

Geissoschizoline **(7)** is an alkaloid isolated from *Geissospermum vellosii*emerges (Apocynaceae family) as a possible multi-target prototype that can be very useful in preventing neurodegeneration and restoring neurotransmission [15].

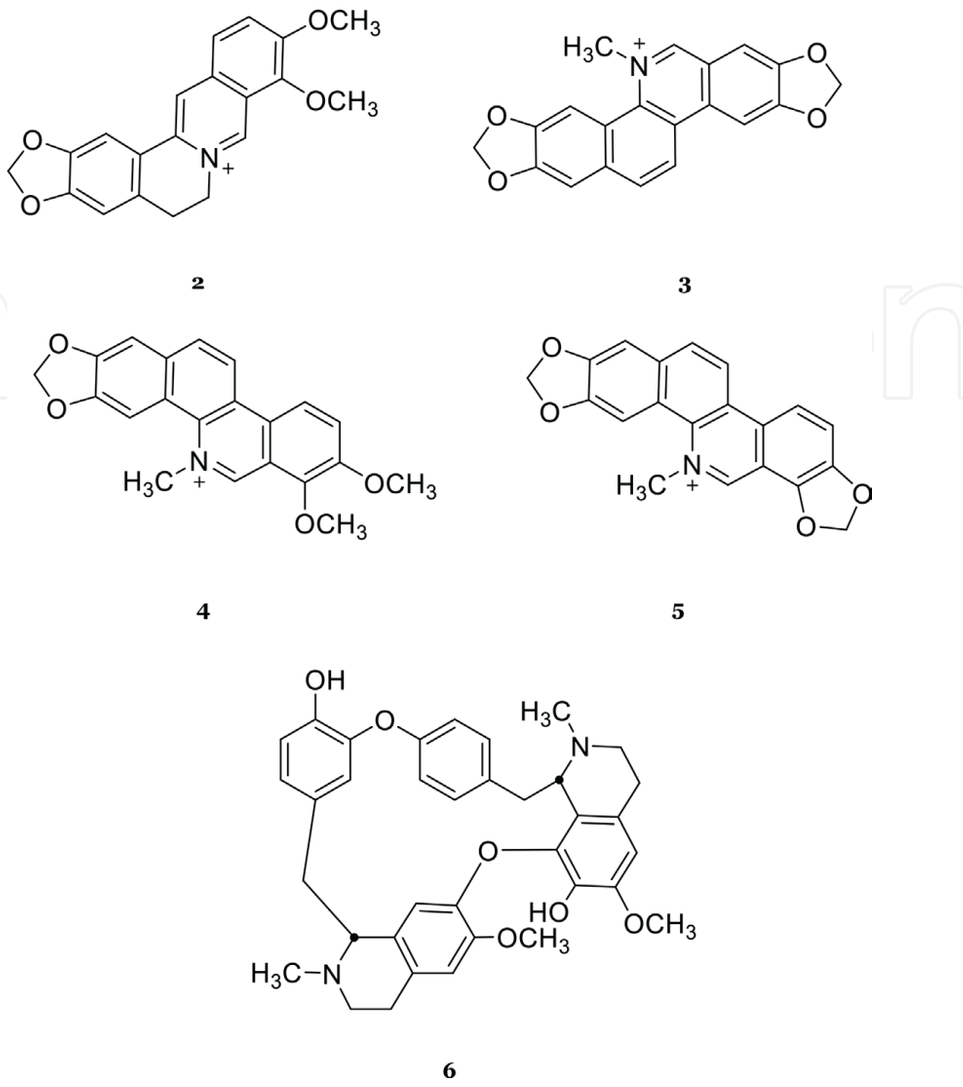

Figure 2.
Berberine (2), avicine (3), Chelerythrine (4), sanguinarine (5), and Aromoline (6).

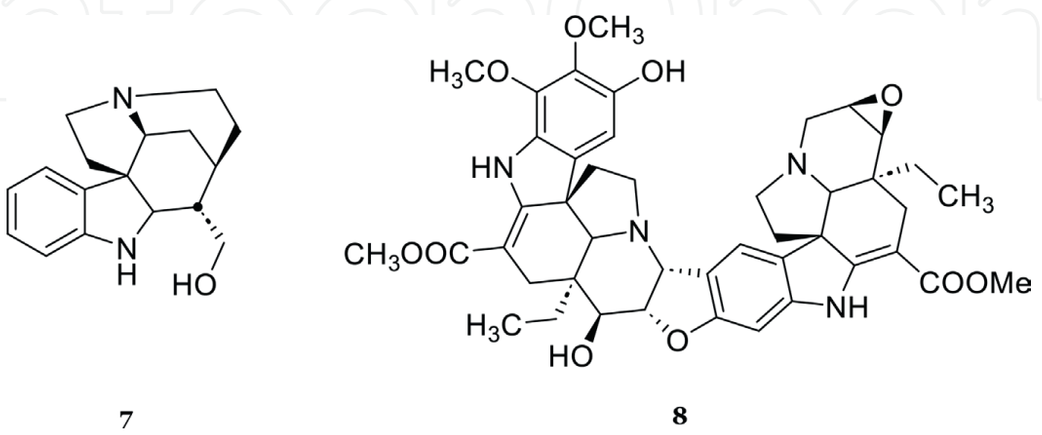

Figure 3.
Geissoschizoline (7) and Conophylline (8).

Neurodegenerative diseases are caused by nerve cell degeneration or death, and it was reported that autophagy is crucial for the prevention of such diseases. Conophylline **(8)**, isolated from *Ervatamia microphylla* (Apocynaceae family) leaves, was found to activate autophagy and suppress protein aggregation to protect the neural cells from cell death (**Figure 3**) [16].

2.4 Quinazoline alkaloids: Vasicinone and dehydroevodiamine

Quinazoline alkaloids belong to the N-based heterocyclic chemical class. To date, around 150 naturally occurring quinazoline alkaloids have been isolated from various plant species as well as animals and microbes; many are biogenetically generated from anthranilic acid. Vasicine was the first quinazoline alkaloid discovered, isolated from *Adhatoda vasica* (Acanthaceae family) and later from additional species [31]. Vasicinone **(9)**, is a vasicine autooxidation product. It demonstrates a neuroprotective mechanism in paraquat-induced Parkinsonian modalities in SH-SY5Y cells [17].

Dehydroevodiamine **(10)** is one of the bioactive components of *Evodiae Fructus* (Rutaceae family), which is widely used in traditional Chinese medicine. *Evodiae fructus* (Wuzhuyu in Chinese) is traditionally used for the treatment of various conditions, including migraine and central nervous system diseases [18]. Dehydroevodiamine **(10)** is the main component of *Evodiae fructus* for its neuroprotective action. Dehydroevodiamine **(10)** is highly permeable through the blood brain barrier and has a protective effect on Alzheimer's disease through its inhibitory effect on acetylcholine esterase (AChE). Clinical results on dehydroevodiamine **(10)** suggest that it's a potential drug candidate for stress-induced depression, neuronal death, and memory impairment [18].

In addition, chemical modification of dehydroevodiamine **(10)** results in carboxydehydroevodiamine. HCl (cx-DHE), which has a better water solubility, bioavailability, and effect on memory impairment. Through several clinical models in mice, the results suggested that cx-DHE is a promising drug candidate that could prevent the progression of Alzheimer's disease pathology (**Figure 4**) [18].

2.5 Protoalkaloids: Capsaicin

Capsaicn **(11)** is a pungent and irritant alkaloid isolated from *Capsicum annuum* (Solanaceae family). It's considered a protoalkaloid as it has

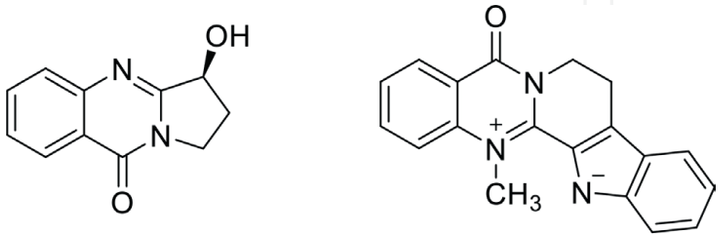

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Figure 4.
Vasicinone (9) and Dehydroevodiamine (10).

non-hetercyclic nitrogen that comes from the amino acid precursors (phenylalanine and valine) [19].

It was previously reported that consumption of a capsaicin-rich diet was associated with better cognition. A recent study found that capsaicin **(11)** has a preventive effect on Alzheimer's disease by promoting the maturation of disintegrin and metalloproteinase 10 and also alleviating other Alzheimer's disease-type pathologies, such as neurodegeneration, tau hyperphosphorylation, and neuroinflammation [19]. These results suggest that supplementation with capsaicin **(11)** and chili peppers could be useful for the prevention and treatment of Alzheimer's disease. In addition, capsaicin **(11)** was found to protect the neural cells and reduce apoptosis by down-regulating Actg1 and up-regulating Gsta2 in the 6-6-hydroxydopamine (6-OHDA)-induced Parkinson's disease cell model (**Figure 5**) [20].

2.6 Carbazole alkaloids: Clauselansiumines A and B

Clauselansiumines A **(12)** and B **(13)** are two new geranylated carbazole alkaloids found in the stem and leaves of *Clausena lansium* (family Rutaceae). The alkaloids were unambiguously determined by spectral analysis, and their neuroprotective effect for Parkinson disease was tested against 6-hydroxydopamine induced cell death in human neuroblastoma and compared with curcumin as a positive control [21].

Clauselansiumines A **(12)** and B **(13)** displayed significant neuroprotective activity with an EC_{50} equal to 0.48 ± 0.04 μM and 0.98 ± 0.08 μM, respectively, which is more potent than the positive control that possessed an EC_{50} value of 6.03 ± 0.10 μM.

The structure activity relationship studies of clauselansiumines A **(12)** and B **(13)** and other geranylated carbazole alkaloids highlight the importance of the isopentenyl group at C-2′ and the methoxy group at positions 7 and 8 for the neuroptotective

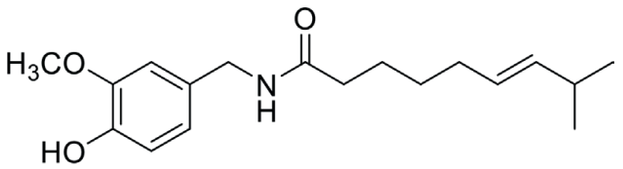

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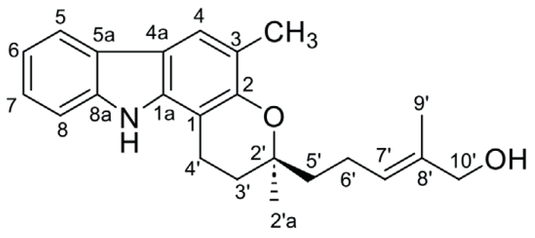
Figure 5.
Capsaicin (11).



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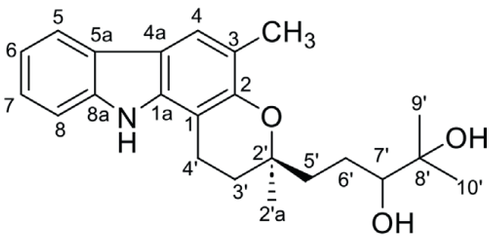

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Figure 6.
Clauselansiumines A (12) and B (13).

activity [21]. In conclusion, the geranylated carbazole alkaloids separated from *C. lansium* could be considered promising candidates for therapeutic purposes in Parkinson's disease and other neural degenerative diseases (**Figure 6**).

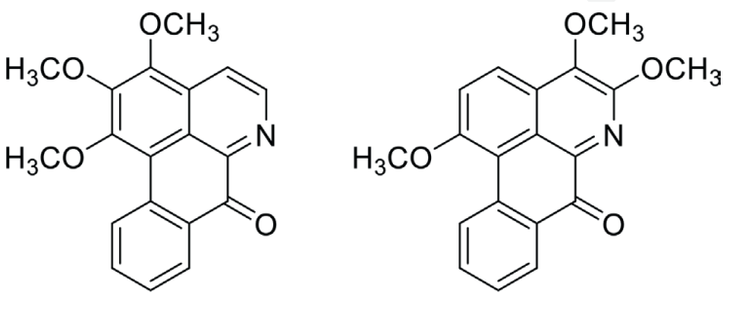
2.7 Aporphine alkaloids

Aporphine alkaloids are a group of naturally occurring compounds with an aporphine nucleus isolated from several plant families such as Annonaceae, Papaveraceae, Ranunculaceae, and others. Recent work on the roots of *Artabotrys spinosus* (Annonaceae family) yielded the isolation of several aporphine alkaloids, of which two compounds **(14)** and **(15)** showed promising inhibitory activity towards AChE and BChE [22]. The *in silico* study confirmed the experimental results and supported the idea that compounds **(14)** and **(15)** are potential candidates for the treatment of Alzheimer's disease (**Figure 7**) [22].

2.8 Norditerpenoid alkaloids (C18 and C19): Lappaconitine, 3-O-acetylaconitine, bulleyaconitine A, and methyllycaconitine

The majority of norditerpenoid alkaloids (NDAs) are isolated from the genera Delphinium and Aconitum, and they are of pharmacological importance. NDAs have a complex hexacyclic structure (A, B, C, D, E, and F). Despite the chemical similarity between NDAs, they display various pharmacological actions, and such variety encourages researchers to work on their structure activity relationship [23]. Lappaconitine **(16)** is the first C_{18} NDA to be reported from *Aconitum septentrionale* Koelle in 1895 and the most successful NDA in terms of clinical application [23]. Lappaconitine **(16)** acts as a voltage gated sodium channel blocker and has a potent non-addictive analgesic effect that is comparable to morphine with an ED_{50} = 3.5 mg/kg [24]. The structure activity relationship studies highlight the importance of the benzoyl ester moiety and the amide group for the activity [23]. Based on the lappaconitine structure activity relationship, several lappaconitine **(16)** analogues were synthesized by replacing the amide moiety with different amides and sulphonamides; this strategy was successful in getting lead compounds as potential analgesics with comparable activity and lower toxicity to lappaconitine **(16)** [25].

3-*O*-acetylaconitine **(17)** and crassicauline A **(18)** are C_{19} NDAs isolated from *Aconitum* spp. They have a similar chemical structure to lappaconitine **(16)** but display an opposite pharmacological action as they keep VGSCs in their open state



14 **15**

Figure 7.
Aporphine alkaloids (14) and (15).

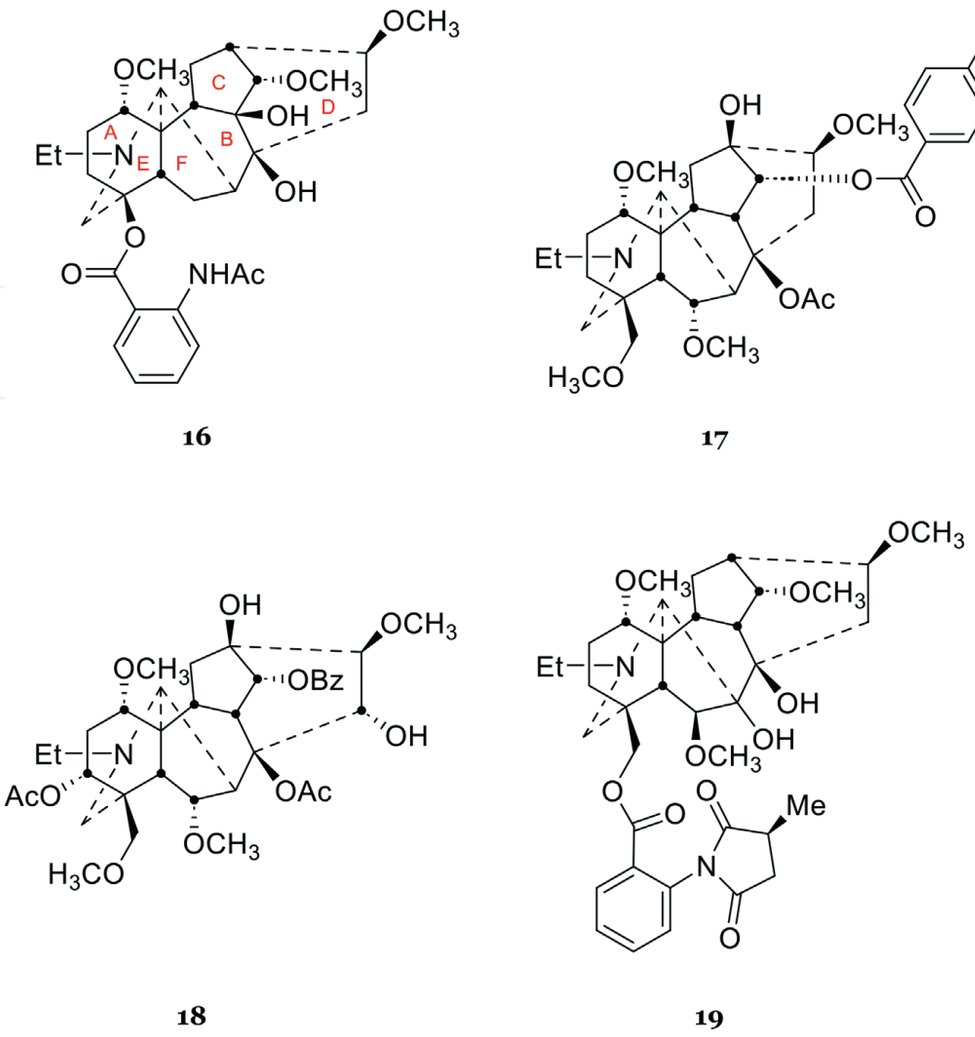


Figure 8.
Lappaconitine (16), 3-O-Acetylaconitine (17), Crassicauline A (18), and Methyllycaconitine (19).

conformation, and they exhibit a non-addictive potent analgesic activity that is comparable to morphine, where 3-*O*-acetylaconitine **(17)** and crassicauline A **(18)** have ED_{50} values of 0.16 and 0.087 mg/kg, respectively. 3-O-acetylaconitine **(17)** and crassicauline A **(18)** were introduced in China into clinical use in the 1980s as analgesic agents [23].

Methyllycaconitine (MLA) **(19)** is a C_{19} alkaloid that was first reported from *Delphinium brownii* Rydb by Manske in 1938. Methyllycaconitine **(19)** is one of the most potent competitive antagonists of α7-nicotinic acetylcholine receptors (nAChRs) with an IC_{50} value of 2 nM [23]. As the total synthesis of MLA **(19)** has not been achieved yet, the synthesis of simple small analogues could be useful to achieve better structure activity relationship understanding and possibly to identify potential candidates for the treatment of several neurodegenerative diseases, including Alzheimer's disease.

Structure activity relationship studies on MLA **(19)** showed that the neopentyl ester side-chain and the piperidine ring *N*-side chain are important features in MLA **(19)** activity [26]. The synthesis of several AE-bicyclic analogues of MLA **(19)** was reported recently, possessing different nitrogen and ester side chains. The antagonist effects of these analogues on human α7 nAChRs showed promising results that

suggest that further optimization and research may enhance the activity of this analogue model (**Figure 8**) [26].

3. Conclusion and future perspective

There are many drugs that have been used to treat neurodegenerative illnesses, but none of them have been able to prevent the disease from getting worse. Instead, they have caused a lot of side effects. Several neurodegenerative illnesses can be treated with natural alkaloids that continue to grow stronger. Analysis of the physicochemical properties of alkaloids showed that most of them follow the Lipinski rules of drug likeness. But only a few alkaloids are widely used in clinical practice. Because natural alkaloids give patients hope that neurodegenerative diseases can be slowed down, it is very important to plan clinical trials for these kinds of compounds that have not even been tried in clinical trials yet. Also, the blood-brain barrier is a key component of keeping substances from going into the brain, and it needs more attention. Meanwhile, it's easy to see why the development of possible candidates into therapeutic leads has stalled because of problems with compounds that come from nature, such as low extraction yields and safety profiles. More studies have to be done on them before they can be used as therapeutics.

Conflict of interest

The authors declare no conflict of interest.

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