

# NEUROPROTECTIVE POTENTIAL OF ZEPHYRANTHES SPECIES AND THEIR BIOACTIVE CONSTITUENTS IN NEURODEGENERATIVE DISORDERS: MECHANISTIC INSIGHTS AND THERAPEUTIC PERSPECTIVES

Ambily Scaria<sup>1,2</sup>, Elphine Prabaha A<sup>1\*</sup>, Siju E.N.<sup>3</sup>

<sup>1</sup> Chettinad School of Pharmaceutical Sciences, Chettinad Hospital and research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Tamilnadu, India

<sup>2</sup> Department of Pharmacology, St. John's College of Pharmaceutical Sciences and Research, Kattappana-685508, Kerala, India

<sup>3</sup> Department of Pharmacology, College of Pharmaceutical Sciences, Government Medical College, Kannur-670503 Kerala, India

\*Corresponding author: Elphine Prabaha A, Email address: elphineprabaha@care.edu.in

## ABSTRACT

Neurodegenerative disorders, particularly Alzheimer's disease (AD), represent a major global health challenge due to their increasing prevalence, progressive nature, and limited therapeutic options. Current pharmacological therapies mainly provide symptomatic relief and are often associated with limited efficacy and adverse effects. Consequently, there is growing interest in medicinal plants and natural products possessing multi-target therapeutic potential. The genus *Zephyranthes* (family Amaryllidaceae), commonly known as rain lilies, is a rich source of biologically active phytoconstituents, especially Amaryllidaceae alkaloids, which exhibit diverse pharmacological activities including neuroprotective, antioxidant, anti-inflammatory, and acetylcholinesterase inhibitory effects.

This review summarizes the phytochemical profile, traditional uses, and neuroprotective potential of different *Zephyranthes* species and their bioactive constituents in the management of neurodegenerative disorders. Major alkaloids such as galantamine, lycorine, haemanthamine, narciclasine, and related compounds have demonstrated promising effects through modulation of multiple signalling pathways associated with neurodegeneration, including cholinergic dysfunction, oxidative stress, neuroinflammation, apoptosis, protein aggregation, and impaired neurogenesis. In addition to alkaloids, phenolic compounds and flavonoids from *Zephyranthes* species contribute significantly to their antioxidant and anti-inflammatory activities.

The evidence discussed in this review highlights the therapeutic relevance of *Zephyranthes* as a potential source of multi-target neuroprotective agents. However, further experimental, toxicological, pharmacokinetic, and clinical investigations are necessary to validate their efficacy and safety for the development of novel therapeutics against Alzheimer's disease and other neurodegenerative disorders.

**KEYWORDS:** *Zephyranthes*; Neuroprotection; Alzheimer's disease; Neurodegenerative disorders; Amaryllidaceae alkaloids

## 1. INTRODUCTION

According to WHO, the number of people living with dementia across the world is expected to rise from 55 million in 2019 to 139 million in 2050. World Alzheimer's report mentions dementia as the seventh leading cause of mortality and expects the costs associated with dementia to rise more than double from US\$1.3 trillion per year in 2019 to 2.8 trillion dollars by 2030<sup>1</sup>. Neurodegenerative diseases (NDDs) become a leading cause of debility and death, especially in low- and middle-income countries due to population growth, and genetic, environmental, and age-related factors<sup>2</sup>.

Despite significant research, finding a definitive cure for Alzheimer's disease (AD) has indeed proven to be challenging. The two main classes of FDA-approved medications for AD currently in the market are cholinesterase inhibitors (ChEI's) like Rivastigmine, Donepezil, and Galantamine and N-methyl-D-aspartate (NMDA) receptor antagonist memantine. ChEI enhances the levels of acetylcholine, a neurotransmitter involved in memory and learning, by inhibiting its breakdown by cholinesterase (ChE). Apart from inhibiting ChE, Galantamine was able to modulate nicotinic receptors, further enhancing cholinergic function. NMDA receptor antagonist memantine helps to modulate glutamate levels, thus preventing excitotoxicity and neuronal dysfunction. These medications primarily aim to manage and alleviate the symptoms associated with AD, such as cognitive decline and memory loss, but are unable to alter the underlying disease process or provide a cure<sup>3</sup>.

The use of alternative systems of medicine, including herbal preparations, has a long history and is still prevalent in many cultures around the world. These systems often encompass traditional practices, holistic approaches, and natural remedies derived from plants and other sources. There has been a growing interest in alternative medicine nowadays due to concerns about rising adverse effects<sup>4</sup>.

Due to the complex pathology of neurodegenerative diseases, mono-target therapy fails often in treating them and thus nutraceuticals with multiple natural ingredients that can target multiple signaling pathways are in the spotlight in treating neurodegenerative diseases. This review article aims to explore the potential ability of *Zephyranthes* and its phytoconstituents in Alzheimer's disease by targeting the signaling pathways underlying the pathogenesis of the disease and its validity as a better treatment option.

## 2. Genus *Zephyranthes*: Occurrence

The family Amaryllidaceae consists of about 82 subordinate taxa with almost 2258 accepted species of monocotyledonous, bulbous flowering plants distributed in three subfamilies namely Agapanthoideae, Allioideae, and Amaryllidoideae. *Zephyranthes* Herb. is a genus belonging to the Amaryllidaceae family within the order Asparagales with almost 90 species, commonly known as 'rain lily'<sup>5,6</sup>. According to the literature, there are over 500 Amaryllidaceae alkaloids with proven medicinal value found in warm-temperate and tropical regions of America and Antilles<sup>7</sup>.

### 2.2. Traditional uses

*Zephyranthes* Herb. have been used traditionally in several countries since ancient times. *Zephyranthes parvula* Killip was used in the history of Peru for treating tumors and *Zephyranthes rosea* Lindl. was used in China for the treatment of breast cancer. *Zephyranthes candida* Herb. has been employed for the treatment of diabetes mellitus in Africa, Poliovirus in Nigeria, and infantile convulsions, tetanus, and epilepsy in China<sup>7-9</sup>. Bulb extracts of *Zephyranthes rosea* and *Zephyranthes flava* were used for the management of Diabetes mellitus, ear, chest, and viral infections in India<sup>7</sup>. *Zephyranthes carinata* was reported to be used in Toba medicine in Argentina for acne, pimples, warts, mycosis, chicken pox, and measles<sup>10</sup>.

## 3. Phytochemistry of genus *Zephyranthes*

There were several reports on the phytochemical studies of different *Zephyranthes* genus. However, the majority of attention in phytochemical studies has been given to analysing alkaloids, with little regard for other constituents of this genus.<sup>7, 8, 11-38</sup>

### 3.1. Alkaloids

Alkaloids are organic compounds derived from amino acids and contain nitrogen. They have a wide range of activities, including neuroprotective, cardioprotective, anticancer, anti-inflammatory, anti-hypertensive, and anti-diabetic actions<sup>39, 40</sup>. All the members of the genus *Zephyranthes* are rich sources of isoquinoline alkaloids, also known as Amaryllidaceae alkaloids. Recent investigations of the phytochemistry of Amaryllidaceae alkaloids have led to the development of a new 12-type classification system based on their ring systems including norbelladine type, lycorine type, homolycorine type, crinine and haemanthamine type, tazettine type, montanine type, plicamine type, graciline type, galanthindole type, galanthamine type, phenanthridone and phenanthridine type and other minor species populations based on their ring systems<sup>41</sup>. Despite the differences in their structure, all Amaryllidaceae alkaloids are formed biogenetically by intramolecular oxidative coupling of norbelladine<sup>40</sup>.

The majority of reported Amaryllidaceae alkaloids of the genus *Zephyranthes* belongs to the Lycorine, homolycorine, galanthamine, crinine, haemanthamine, narciclasine, tazettine, plicamine and pancratistatin skeleton types<sup>42</sup>. Recently, a Narcikachnine-type alkaloid, Narcieliine, mesembrine type alkaloid, 3'- dimethoxy-6-epimesembranol and a graciline-type alkaloid, Zephyranine B was isolated from *Zephyranthes citrina*, *Zephyranthes fosteri*, and *Zephyranthes candida* respectively. Zephyranine A from *Zephyranthes candida* represents the first naturally occurring 10b,11-seco-crinine type alkaloid. Among the Amaryllidaceae alkaloids, Galanthamine has been introduced into the market for treating mild-moderate symptoms of Alzheimer's disease whereas lycorine-, haemanthamine- and narciclasine-type alkaloids have been used as lead molecules in anticancer research<sup>43-47</sup>.

### 3.2. Phenolic compounds

Phenolics are a group of polyphenolic compounds that are commonly found in plants. This group includes phenolic acids, flavonoids, tannins, stilbenes, and lignans. These molecules have potent antioxidant properties and can help prevent diseases resulting from oxidative stress.<sup>48</sup> There were a few reports on the presence of phenolic compounds in *Zephyranthes* genus. Both the methanolic extract of *Zephyranthes citrina* and the ethanolic extract of *Zephyranthes candida* reported the presence of significant amounts of total phenols along with moderate amounts of total flavonoids and tannins<sup>49, 50</sup>

### 3.3. Flavonoids

Flavonoids are important polyphenolic compounds commonly found in fruits, herbs, roots, vegetables, flowers, and seeds. They have been extensively used as neuroprotective, anticancer, antiviral, antimalarial, antiangiogenic, antimicrobial, anti-inflammatory, and antioxidant agents. Anthoxanthins (flavanone and flavanol), flavanonols, flavans, chalcones, isoflavonoids, and anthocyanidins are the different subgroups of flavonoids<sup>51-53</sup>.

*Zephyranthes flava* bulbs, *Zephyranthes candida*, and *Zephyranthes ajax* are rich sources of flavans. Flavonoids isolated from the whole plants of *Zephyranthes candida* showed significant anti-inflammatory properties and efficacy against poliovirus<sup>14, 28, 35, 52, 54</sup>.

### 3.4. Volatile components

Among various members of *Zephyranthes*, *Zephyranthes candida* flowers extracted using headspace-solid phase micro-extraction (HS-SPME) and analyzed by gas chromatography-mass spectrometry (GC-MS) reported the presence of a wide variety of volatile components, with the major constituents being 1-hexanol, methyl heptanoate, hexyl acetate, 2-acetyl pyrrole, methyl- $\alpha$ -D-rhamnopyranoside, phenethyl alcohol, heptanoic acid, and 1-octanol<sup>55</sup>. Later seventeen volatile compounds were also identified in *Zephyranthes candida* flowers, with 16 terpenoids and a non-terpenoid alkene (E)-9-octadecene<sup>56</sup>.

### 3.5. Ceramides

Ceramides are a diverse group of sphingolipids that are crucial in maintaining the skin's water permeability barrier function. They also act as signaling molecules in programmed cell death and apoptosis. Recent phytochemical studies on *Zephyranthes candida* have reported the presence of ceramides, such as Candidamide A, Candidamide B, Zephyranamide A, B, C, and D, which were the first ceramides reported in Amaryllidaceae. Among them, Candidamide A and Candidamide B showed moderate activity against bacteria and fungi, including *Staphylococcus aureus*, *Escherichia coli*, *Aspergillus niger*, *Candida albicans*, and *Trichophyton rubrum*.<sup>57-59</sup>

### 3.6. Glycosides

There were only limited reports regarding the presence of glycosides in *Zephyranthes*. A narciclasine glycoside, narciclasine-4-O- $\beta$ -D-xylopyranoside was reported from the n-butanol fraction of *Zephyranthes minuta*<sup>60</sup>.

### 3.7. Other compounds

Apart from the above-mentioned phytoconstituents *Zephyranthes* genus consists of several other compounds like p-hydroxybenzaldehyde, and sterols<sup>7</sup>. Two undescribed constituents, Zephyranthine-6-one and 3-O-deacetyl-sternbergine were also isolated from *Zephyranthes candida* recently<sup>61</sup>.

## 4. Modulation of multiple signalling pathways of neurodegeneration by genus *Zephyranthes* and their bioactive constituents

### 4.1. Neuroprotective activities of extracts from *Zephyranthes* Species

Members of the Amaryllidaceae family, including the genus *Zephyranthes* exhibit a variety of physiological effects like Acetylcholine esterase (AChE) Inhibition, analgesic, anti-bacterial, anti-fungal, anti-malarial, anti-tumour, anti-viral and cytotoxic activities, of which the most important is AChE Inhibition<sup>7</sup>. Scientific evidence suggests that, apart from providing symptomatic relief ChEIs can provide neuroprotective effects by modulating and activating many cell survival pathways downstream<sup>62</sup>. Thus, modulation of the Acetylcholine (ACh) level helps in mitigating cognitive impairments in AD, and ChEIs from the Amaryllidaceae family are in the spotlight for Alzheimer's research.

Alkaloidal extracts and alkaloids of several species of *Zephyranthes* belonging to the Amaryllidaceae family were reported to possess significant AChE inhibition making them promising candidates as ChEIs in AD research<sup>47,63-71</sup>. Apart from inhibiting choline esterases, several researchers have also reported the antioxidant potential of *Zephyranthes* plants. They conducted studies to assess the antioxidant capacity of these plants by evaluating their ability to scavenge DPPH and ABTS radicals. The findings of these studies provide valuable insights into the antioxidant properties and free radical-scavenging potential of *Zephyranthes* species. *Zephyranthes rosea* flower extract and silver oxide nanoparticles (Ag<sub>2</sub>O NPs) were tested for their antioxidant activity using DPPH assay. Both, the extract and silver oxide nanoparticles, exhibited significant anti-oxidant activity with an increase in concentration. Also, the Ag<sub>2</sub>O NPs showed better antioxidant activity than the *Z. rosea* flower extract<sup>72</sup>.

The methanolic extract of *Zephyranthes citrina* (MEZ) was screened for its in vitro antioxidant activity using DPPH assay. MEZ showed excellent free radical scavenging activity (88%), possibly due to the presence of several antioxidant phytochemicals like flavonoids and phenolic compounds, particularly methyl gallate and gingerol. Methyl gallate might have upregulated the antioxidant enzymes thus protecting different tissues against the deleterious effects of toxic compounds while Gingerol inhibited lipid peroxidation and provided an antioxidant effect by its free radical scavenging activity<sup>73</sup>.

*Zephyranthes* species possess potent anti-inflammatory properties; however, there are limited studies on their anti-inflammatory potential. Alkaloidal fraction (10 $\mu$ g/ml) of *Zephyranthes carinata* (bulb) showed the highest anti-inflammatory potential with a decrease in IL-6 production by 90.8% in keratinocytes exposed to ultraviolet B radiation<sup>74</sup>. Also, alkaloidal fractions of *Zephyranthes carinata* (bulbs and leaves) exhibited neuroprotective potential in an in vitro excitotoxicity model and a triple transgenic model of Alzheimer's disease (AD), and among them, alkaloidal fractions of bulbs were more efficient in protecting neurons against Glu-mediated excitotoxicity, improving learning and spatial memory, reducing tauopathy and astrogliosis, and regulating inflammatory processes.<sup>75</sup>

### 4.2. Amaryllidaceae alkaloids as neuroprotective agents

#### 4.2.1. Galanthamine-type alkaloids

Cholinergic transmission plays a vital role in neuronal plasticity and survival and Acetylcholine (ACh) is the major neurotransmitter released by cholinergic neurons involved in learning and memory.<sup>76</sup> However, Acetylcholine is rapidly degraded by Acetylcholine esterase (AChE) into choline and acetate which can lead to cognitive impairment<sup>77</sup>. Choline

esterase inhibitors (ChEIs) can maintain proper levels of ACh by decreasing its breakdown and allowing a higher occupancy rate and longer duration at its receptor<sup>78</sup>.

Galantamine is a well-known Amaryllidaceae alkaloid available in the market for the symptomatic treatment of AD<sup>79</sup>. Most studies have reported that amaryllidaceae alkaloids of the galanthamine and lycorine skeleton types were more effective than others in inhibiting AChE<sup>63, 80</sup>. The potency of Galanthamine for AChE was found to be consistent with an average IC<sub>50</sub> value of 1.5 μM in several studies<sup>81</sup>. Sanguinine (O-desmethyl galanthamine) was found to be ten times more potent than galanthamine (IC<sub>50</sub>=0.1 μM)<sup>82</sup>.

Apart from inhibiting AChE, Galantamine also enhances the expression and activation of α7nAChRs and acts as an allosteric enhancer of human α4/β2 neuronal nAChR<sup>83</sup>. Several studies proposed that Galantamine exhibits a dual mode of action on nAChR i.e, at low concentrations (≤ 1μM), it acts as a positive allosteric modulator (PAM), while at higher concentrations (> 10μM) it behaves as an antagonist. However, a few studies have also reported that galantamine inhibits nAChRs<sup>84, 85</sup>. However, further studies are necessary to resolve these discrepancies.

There were previous studies about the interplay between AChE and neuroprotection. However, potent AChE blockers like Tacrine and Physostigmine were not able to protect rat cortical neurons from glutamate toxicity<sup>86</sup>. This suggests that neuroprotective activity exhibited by AChEIs are not directly related to AChE inhibition<sup>87</sup>. Although there are several studies about the neuroprotective ability of AChE inhibitors, the results are mostly controversial.

Galantamine was able to prevent cell death induced by Aβ<sub>1-40</sub> and thapsigargin in human neuroblastoma cell line SH-SY5Y as well as in bovine chromaffin cells in a concentration-dependent manner. Galantamine caused sustained elevation of density of α7nAChRs, cytosolic Ca<sup>2+</sup> levels, and expression of anti-apoptotic protein Bcl-2. These protective effects of Galantamine were reversed by α-bungarotoxin and suggest that Galantamine can prevent apoptotic cell death by inducing neuroprotection by upregulation of α7nAChRs and Bcl-2 levels<sup>88</sup>.

This mechanism of Galantamine was supported by another study in the human neuroblastoma cell line SH-SY5Y. They also supported that the neuroprotective effect of Galantamine was due to its interaction with α7nAChR and downstream activation of the Phosphoinositide 3 kinase (PI3K)-Akt pathway with increased expression of anti-apoptotic protein Bcl-2. An interruption in this pathway by an α7nAChR antagonist, Methyllycaconitine (MLA), selective PI3K-Akt inhibitor LY294002 and Bcl-2 antagonist HA 14-1 reversed the effects of Galantamine<sup>89</sup>.

α7nAChRs bind with high affinity to Aβ peptides and can result in intraneuronal accumulation of Aβ<sub>1-42</sub> and Aβ induced tau-protein phosphorylation<sup>90</sup>. The neuroprotective activity demonstrated by Galantamine in Aβ<sub>1-40</sub> and Aβ<sub>25-35</sub> induced apoptosis in SH-SY5Y cells was associated with α7nAChR<sup>89, 91</sup>. Moreover, Galantamine inhibited Aβ<sub>1-42</sub> induced apoptosis by enhancing α7nAChR expression by activating the JNK Pathway as well as autophagosome biogenesis and autophagy by inhibiting the Akt pathway. Furthermore, these effects can be reproduced by α7nAChR overexpression even in the absence of Galantamine<sup>88</sup>.

In addition to improving cognitive and behavioural symptoms, Galantamine has disease-modifying and neuroprotective properties. Recent results have shown that high-dose treatment with Galantamine delayed Aβ plaque formation and reduced gliosis in 5XFAD mice<sup>92</sup>. Galantamine exhibited neuroprotective effects by preventing the release of reactive oxygen species (ROS), nitrite generation, and loss of mitochondrial activity in an H<sub>2</sub>O<sub>2</sub>-induced oxidative stress model in SK-N-SH cells<sup>93</sup>.

Cognitive impairment in AD is also linked with neurodegeneration and a subsequent decline in levels of growth factors like brain-derived neurotrophic growth factor, nerve growth factor, vascular endothelial growth factor, and insulin-like growth factors (IGF-1 and IGF-2). Studies proposed that neurogenesis can act as a defense strategy against neurodegeneration in AD. Galantamine enhanced neurogenesis via activating M<sub>1</sub> muscarinic and α7nAChR and upregulating IGF-2 levels, promoting the survival of immature cells in the granule cell layer<sup>94</sup>.

#### 4.2.2. Lycorine-type alkaloids

Lycorine-type alkaloids are the most diverse group among amaryllidaceae alkaloids. Lycorine exhibited several pharmacological activities like anti-viral, anti-oxidant, anti-cancer, and anti-inflammatory effects<sup>95-98</sup>. Lycorine functions as a natural antioxidant by inhibiting lipid peroxidation and displaying high scavenging activity for free radicals, hydrogen peroxide, and superoxide anions.<sup>96</sup> Lycorine reduces inflammatory cytokines and oxidative stress markers by inhibiting the HMGB1/TLRs/NF-κB pathway<sup>98</sup>. Norbelladine, a precursor of Lycorine, can also inhibit NF-κB activation and associated cyclooxygenases (COX), as well as quench free radicals even at low concentrations.<sup>99</sup>

Although Lycorine exhibits low inhibitory properties towards choline esterases, its acylated and etherified analogues are more effective in inhibiting them.<sup>100-102</sup> Galanthine is a type of lycorine alkaloid found in *Z. carinata*. It is a powerful inhibitor of acetylcholinesterase (AChE), with an IC<sub>50</sub> value of 6.10±0.26 μM. This suggests that the 9-OCH<sub>3</sub> group is an essential component for the activity of lycorine-type alkaloids. Interestingly, the study also found that an N-oxide moiety is a deactivating group for AChE inhibitory activity. 1-O-acetyllycorine has double the AChE inhibitory activity (IC<sub>50</sub>=0.96±0.04μM) compared to Galanthamine (IC<sub>50</sub>=1.9±0.16 μM) when tested with Electric eel AChE.<sup>82, 103</sup> However, it was not effective against human AChE and has an IC<sub>50</sub> > 1000 μM suggesting that different types of AChE enzymes can often result in significant differences in IC<sub>50</sub> values<sup>80</sup>.

Lycorine activates Protein Kinase A (PKA)-mediated Ubiquitin-proteasome system (UPS), promoting α-synuclein clearance in-vitro and in-vivo. It has the potential to treat neurodegenerative diseases like Parkinson's disease, associated with UPS dysregulation and protein aggregation.<sup>104</sup> Lycorine has been found to have potent anti-inflammatory effects by blocking the upregulation of nitric oxide synthase (iNOS) and COX-2 and inhibiting Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), nitric oxide (NO), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α) in RAW264.7 cells. By suppressing the p38 and STAT pathways without interfering with the phosphorylation of the ERK1/2, JNK1/2, and NF-κB pathways, Lycorine was able to increase the survival rate of mice challenged with LPS.<sup>105</sup> Lycorine hydrochloride, which is a salt of lycorine,

has been found to effectively prevent premature cellular senescence caused by stress. It achieves this by enhancing the expression of critical longevity genes, SIRT1 and SIRT6, thereby regulating the Homologous recombination (HR) and Non-homologous end-joining (NHEJ) repair pathways. This study confirms the potential of lycorine hydrochloride as a therapeutic agent for treating age-related illnesses or promoting healthy aging by stabilizing the genome<sup>106</sup>.

#### **4.2.3. Crinine and Haemanthamine type alkaloids**

Due to the higher failure rates encountered by single targeted drugs in AD, novel aromatic esters were developed from haemanthamine and among them four semisynthetic derivatives of haemanthamine, namely 11-O-(2-methoxybenzoyl)-haemanthamine, 11-O-(4-nitrobenzoyl)-haemanthamine, 11-O-(4-chlorobenzoyl)-haemanthamine, and 11-O-(2-methylbenzoyl)-haemanthamine, exhibited significant cholinesterase activity and GSK-3 $\beta$  inhibition properties. They also showed the ability to cross the blood-brain barrier via passive diffusion.<sup>107, 108</sup>

Even though Haemanthamine doesn't exhibit a significant choline esterase inhibitory potential, it was able to inhibit  $\alpha 7$ ,  $\alpha 4\beta 2$ , and  $\alpha 3\beta 4$  nAChRs<sup>109</sup>. Haemanthamine-type alkaloids such as Zephyranine B, haemanthamine, haemanthidine, and 11-hydroxy vittatine from *Zephyranthes candida* also exhibited potent anti-inflammatory activity against LPS-induced NO production in macrophages of RAW264.7 and haemanthamine being most active<sup>61</sup>. The anti-inflammatory activity of Haemanthidine was also supported by its activity against Carrageenan-induced paw edema in mice where it shows anti-inflammatory properties greater than that of Indomethacin.<sup>110</sup>

#### **4.2.4. Tazettine-type alkaloid**

Tazettine was able to reduce intracellular ROS by modulating endogenous antioxidant mechanisms and free radical stabilizing activity in a study assessing the photoprotective potential of different HaCaT cells. Tazettine also protected human keratinocytes from ultraviolet-B (UVB)- induced IL-6. Thus, tazettine was found to possess significant antioxidant and anti-inflammatory properties<sup>111</sup>.

#### **4.2.5. Phenanthridone and Phenanthridine type alkaloids**

Narciclasine is an isocarbostryl Amaryllidaceae alkaloid with remarkable activity against AD, cancer, obesity, Rheumatoid arthritis (RA), and inflammation. The modulating effects of Narciclasine in inflammation have been depicted by various experimental results. Published evidence supports the role of AMPK in the regulation of cellular metabolism and its anti-inflammatory and immunosuppressive effects. Narciclasine (NA) was able to suppress T-cell mediated immune reactions by activating AMPK pathway and thus reducing serum cytokine levels<sup>112</sup>. It was also evident that Narciclasine can downregulate Akt/IKK/NF- $\kappa$ B and JNK signalling pathways, and directly inhibit the catalytic activity of IKK $\alpha/\beta$  thus can be a potential candidate for alleviating neuroinflammation in neurodegenerative disorders<sup>113</sup>. By activating Toll-like Receptor 4 (TLR4)/Nuclear factor (NF)- $\kappa$ B/Cyclooxygenase 2 (Cox2) signaling pathway Narciclasine was able to exert an anti-inflammatory effect<sup>114</sup>. Narciclasine offered beneficial effects in the treatment of AD by improving disrupted memory and inhibiting amyloid plaque formation by downregulating amyloid precursor protein and secretases<sup>115</sup>

#### **4.2.6. Other alkaloids**

Plicamine alkaloids Zephygranditine A and B displayed anti-inflammatory activity by inhibiting the production of NO and COX-1/COX-2<sup>13</sup>

#### **4.2.7. Flavanoids as anti-inflammatory agents**

Flavanoids are a class of phytochemical compounds widely distributed in plants, however are rare in the genus *Zephyranthes*. Flavanoids from *Zephyranthes candida* exhibited activity against LPS-induced NO production in RAW 264.7 mouse macrophages thus emphasizing the anti-inflammatory properties of flavonoids present in *Zephyranthes*<sup>52</sup>.

## **5. CONCLUSION**

The genus *Zephyranthes* represents a promising source of bioactive phytoconstituents with significant neuroprotective potential against neurodegenerative disorders, particularly Alzheimer's disease. Various species of *Zephyranthes* are rich in Amaryllidaceae alkaloids such as galantamine, lycorine, haemanthamine, narciclasine, and related compounds, along with phenolics and flavonoids that exhibit antioxidant, anti-inflammatory, cholinesterase inhibitory, and neuroprotective activities. These phytochemicals act through multiple signalling pathways involved in neurodegeneration, including modulation of cholinergic neurotransmission, inhibition of oxidative stress, suppression of neuroinflammation, regulation of apoptotic pathways, enhancement of neurogenesis, and reduction of protein aggregation.

Among these constituents, galantamine has already gained clinical importance as an approved therapeutic agent for Alzheimer's disease, highlighting the medicinal relevance of Amaryllidaceae alkaloids. In addition, several other alkaloids and extracts from *Zephyranthes* species have demonstrated encouraging in vitro and in vivo neuroprotective effects, suggesting their potential as multi-target therapeutic agents for complex neurodegenerative conditions.

Although existing findings strongly support the therapeutic prospects of *Zephyranthes*, comprehensive pharmacological, toxicological, mechanistic, and clinical studies are still required to validate their efficacy and safety. Future research focusing on isolation of novel compounds, molecular target identification, pharmacokinetic profiling, and clinical evaluation may facilitate the development of effective plant-derived therapeutics for neurodegenerative diseases.

## **ETHICAL ISSUES**

None to be declared

## **ACKNOWLEDGEMENT**

The authors gratefully acknowledge the authorities of their institutions for providing basic facilities and support.

## FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## CONFLICT OF INTERESTS

Authors declare no conflict of interests

## REFERENCES

1. World Alzheimer Report 2023 Reducing dementia risk: never too early, never too late.
2. Cummings J, Lee G, Nahed P, Kamar MEZN, Zhong K, Fonseca J, Taghva K (2022) Alzheimer's disease drug development pipeline: 2022. *Alzheimer's and Dementia: Translational Research and Clinical Interventions*. <https://doi.org/10.1002/trc2.12295>
3. Alhazmi HA, Albratty M (2022) An update on the novel and approved drugs for Alzheimer disease. *Saudi Pharmaceutical Journal* 30:1755–1764
4. Wachtel-Galor S, Benzie IFF (2011) *Herbal Medicine: An Introduction to Its History, Usage, Regulation, Current Trends, and Research Needs*, 2nd ed. CRC Press/Taylor & Francis
5. Meerow AW, Fay MF, Guy CL, Li QB, Zaman FQ, Chase MW (1999) Systematics of Amaryllidaceae based on cladistic analysis of plastid sequence data. *Am J Bot* 86:1325–45
6. Taxonomy Browser - NCBI - NLM. <https://www.ncbi.nlm.nih.gov/datasets/taxonomy/tree/?taxon=4668,82256>. Accessed 3 Feb 2024
7. Nguyen KV, Ho DV, Le NT, Van Phan K, Heinämäki J, Raal A, Nguyen HT (2020) Flavonoids and alkaloids from the rhizomes of *Zephyranthes ajax* Hort. and their cytotoxicity. *Sci Rep* 10:22193
8. Singh B KD (2015) Phytochemistry and Pharmacology of Genus *Zephyranthes*. *Med Aromat Plants (Los Angel)*. <https://doi.org/10.4172/2167-0412.1000212>
9. Pettit GR, Gaddamidi V, Cragg GM (1984) Antineoplastic Agents, 105. *Zephyranthes grandiflora*. *J Nat Prod* 47:1018–1020
10. Ogbole O, Johnson Adeniji A, Ajaiyeoba EO, Festus Rufus Giwa Polytechnic D (2013) African Journal of Biotechnology Anti-poliovirus activity of medicinal plants selected from the Nigerian ethno-medicine. <https://doi.org/10.5897/AJB12.2730>
11. Martínez GJ, Barboza GE (2010) Natural pharmacopoeia used in traditional Toba medicine for the treatment of parasitosis and skin disorders (Central Chaco, Argentina). *J Ethnopharmacol* 132:86–100
12. Ghosal S, Singh SK, Unnikrishnan SG (1987) Phosphatidylpyrrolophenanthridine alkaloids from *Zephyranthes flava*. *Phytochemistry* 26:823–828
13. Yang Q, Lin G, Wang P-H, Zhou M, Zhou D, Cheng Y-Z (2022) Cytotoxic plicamine alkaloids from the whole plants of *Zephyranthes grandiflora*. *J Asian Nat Prod Res* 24:24–30
14. Wang H-Y, Qu S-M, Wang Y, Wang H-T (2018) Cytotoxic and anti-inflammatory active plicamine alkaloids from *Zephyranthes grandiflora*. *Fitoterapia* 130:163–168
15. Zhan G, Zhou J, Liu J, Huang J, Zhang H, Liu R, Yao G (2017) Acetylcholinesterase Inhibitory Alkaloids from the Whole Plants of *Zephyranthes carinata*. *J Nat Prod* 80:2462–2471
16. Zhan G, Liu J, Zhou J, Sun B, Aisa HA, Yao G (2017) Amaryllidaceae alkaloids with new framework types from *Zephyranthes candida* as potent acetylcholinesterase inhibitors. *Eur J Med Chem* 127:771–780
17. Katoch D, Kumar D, Sharma U, Kumar N, Padwad YS, Lal B, Singh B (2013) Zephgrabetaine: A New Betaine-type Amaryllidaceae Alkaloid from *Zephyranthes grandiflora*. <https://doi.org/10.1177/1934578X1300800206> 8:161–164
18. Cahliková L, Valterová I, Macáková K, Opletal L (2011) Analysis of Amaryllidaceae alkaloids from *Zephyranthes grandiflora* by GC/MS and their cholinesterase activity. *Revista Brasileira de Farmacognosia* 21:575–580
19. Katoch D, Kumar S, Kumar N, Singh B (2012) Simultaneous quantification of Amaryllidaceae alkaloids from *Zephyranthes grandiflora* by UPLC-DAD/ESI-MS/MS. *J Pharm Biomed Anal* 71:187–192
20. Cahliková L, Kulhánková A, Urbanová K, Valterová I, Macáková K, Kuneš J (2010) Analysis of amaryllidaceae alkaloids from *Zephyranthes robusta* by GC-MS and their cholinesterase activity. *Nat Prod Commun* 5:1201–1204
21. Ghosal S, Singh SK, Srivastava RS (1986) Alkaloids of *zephyranthes flava*. *Phytochemistry* 25:1975–1978
22. Kojima K, Mutsuga M, Inoue M, Ogihara Y (1998) Two alkaloids from *Zephyranthes carinata*. *Phytochemistry* 48:1199–1202
23. Zephgrabetaine: A New Betaine-type Amaryllidaceae Alkaloid from *Zephyranthes grandiflora* - Deepali Katoch, Dharmesh Kumar, Upendra Sharma, Neeraj Kumar, Yogendra S. Padwad, Brij Lal, Bikram Singh, 2013. <https://journals.sagepub.com/doi/10.1177/1934578X1300800206>. Accessed 3 Feb 2024
24. Rehman MHU, Saleem U, Ahmad B, Rashid M (2022) Phytochemical and toxicological evaluation of *Zephyranthes citrina*. *Front Pharmacol* 13:1007310
25. Kohelová E, Maříková J, Korábečný J, et al (2021) Alkaloids of *Zephyranthes citrina* (Amaryllidaceae) and their implication to Alzheimer's disease: Isolation, structural elucidation and biological activity. *Bioorg Chem*. <https://doi.org/10.1016/J.BIOORG.2020.104567>
26. Kobayashi S, Ishikawa H, Kihara M, Shingu T, Hashimoto T (1977) Isolation of Carinatine and Pretazettine from the Bulbs of *Zephyranthes carinata* HERB. (Amaryllidaceae). *Chem Pharm Bull (Tokyo)* 25:2244–2248
27. Pettit GR, Gaddamidi V, Cragg GM (1984) Antineoplastic agents, 105. *zephyranthes grandiflora*1. *J Nat Prod* 47:1018–1020

28. Oluyemisi OO, Oriabure AE, Adekunle AJ, Ramsay KST, Shyyaula S, Choudhary MI (2015) Bioassay-guided isolation of Poliovirus-inhibiting constituents from *Zephyranthes candida*. *Pharm Biol* 53:882–887
29. Ghosal S, Singh SK, Unnikrishnan SG (1987) Phosphatidylpyrrolophenanthridine alkaloids from *Zephyranthes flava*. *Phytochemistry* 26:823–828
30. Herrera MR, Machocho AK, Brun R, Viladomat F, Codina C, Bastida J (2001) Crinane and lycorane type alkaloids from *Zephyranthes citrina*. *Planta Med* 67:191–193
31. Noviyanti, Martiani I, Perdana F, Rahmaniah (2022) Determination of total phenol and total flavonoid, and antioxidant activities of chocolate leaves (*Zephyranthes candida* (Lindl.) Herb.). *Bali Medical Journal* 11:927–933
32. Kulhánková A, Cahlíková L, Novák Z, MacÁková K, Kuneš J, Opletal L (2013) Alkaloids from *Zephyranthes robusta* Baker and Their Acetylcholinesterase- and Butyrylcholinesterase-Inhibitory Activity. *Chem Biodivers* 10:1120–1127
33. Ghosal S, Ashutosh, Razdan S (1985) (+)-Epimaritidine, an alkaloid from *Zephyranthes rosea*. *Phytochemistry* 24:635–637
34. Yang J-S, Feng X, Chen Y, Zhao X-Z, Wang M, Wang Q-Z, Dong Y-F (2010) [Study on the chemical constituents from the bulbs of *Zephyranthes candida*]. *Zhong Yao Cai* 33:1730–2
35. Ghosal S, Singh SK, Srivastava RS (1985) Flavans from *Zephyranthes flava*. *Phytochemistry* 24:151–153
36. Boit HG, Döpke W, Stender W (1958) Alkaloide aus *Hippeastrum rutilum*, *Lycoris albiflora*, *Zephyranthes andersoniana* und *Sternbergia fischeriana*. *Naturwissenschaften* 45:390
37. Boit H -G, Ehmke H (1955) Alkaloide von *Sprekelia formosissima*, *Galanthus Elwesii*, *Zephyranthes candida* und *Crinum Powellii* (VIII. Mitteil. über Amaryllidaceen-Alkaloide I)). *Chem Ber* 88:1590–1594
38. Chen XY, Bi SF (2022) Identification of Volatile Components of Flowers Of *Zephyranthes Candida* (Lindl.) Herb. *Bangladesh J Bot* 51:175–178
39. Dey A, Mukherjee A (2018) Plant-Derived Alkaloids. In: *Discovery and Development of Neuroprotective Agents from Natural Products*. Elsevier, pp 237–320
40. Hoshino O (1998) The Amaryllidaceae Alkaloids. pp 323–424
41. Jin Z, Xu X-H (2013) Amaryllidaceae Alkaloids. In: *Natural Products*. Springer Berlin Heidelberg, Berlin, Heidelberg, pp 479–522
42. Devkar SP, Otari SS, Ghane SG (2023) Bioactive Compounds and Biological Activities of *Zephyranthes* Species. pp 1–18
43. Roy M, Liang L, Xiao X, Feng P, Ye M, Liu J (2018) Lycorine: A prospective natural lead for anticancer drug discovery. *Biomedicine & Pharmacotherapy* 107:615–624
44. Fürst R (2016) Narciclasine – an Amaryllidaceae Alkaloid with Potent Antitumor and Anti-Inflammatory Properties. *Planta Med* 82:1389–1394
45. Van Goietsenoven G, Andolfi A, Lallemand B, et al (2010) Amaryllidaceae Alkaloids Belonging to Different Structural Subgroups Display Activity against Apoptosis-Resistant Cancer Cells. *J Nat Prod* 73:1223–1227
46. Zhan G, Gao B, Zhou J, Liu T, Zheng G, Jin Z, Yao G (2023) Structurally diverse alkaloids with nine frameworks from *Zephyranthes candida* and their acetylcholinesterase inhibitory and anti-inflammatory activities. *Phytochemistry* 207:113564
47. Kohelová E, Maříková J, Korábečný J, et al (2021) Alkaloids of *Zephyranthes citrina* (Amaryllidaceae) and their implication to Alzheimer's disease: Isolation, structural elucidation and biological activity. *Bioorg Chem* 107:104567
48. Dai J, Mumper RJ (2010) Plant phenolics: extraction, analysis and their antioxidant and anticancer properties. *Molecules* 15:7313–52
49. Prakash J, Vedanayaki S (2019) Organoleptic, fluorescence, qualitative and quantitative analysis of bulb extract of *Zephyranthes citrina*. *J. Pharmacogn. Phytochem.*
50. Noviyanti, Martiani I, Perdana F, Rahmaniah (2022) Determination of total phenol and total flavonoid, and antioxidant activities of chocolate leaves (*Zephyranthes candida* (Lindl.) Herb.). *Bali Medical Journal* 11:927–933
51. Ullah A, Munir S, Badshah SL, Khan N, Ghani L, Poulson BG, Emwas A-H, Jaremko M (2020) Important Flavonoids and Their Role as a Therapeutic Agent. *Molecules*. <https://doi.org/10.3390/molecules25225243>
52. Zhan G, Zhou J, Liu T, Zheng G, Aisa HA, Yao G (2016) Flavans with potential anti-inflammatory activities from *Zephyranthes candida*. *Bioorg Med Chem Lett* 26:5967–5970
53. Rauter AP, Ennis M, Hellwich K-H, Herold BJ, Horton D, Moss GP, Schomburg I (2018) Nomenclature of flavonoids (IUPAC Recommendations 2017). *Pure and Applied Chemistry* 90:1429–1486
54. Nakayama M, Horie T, Tsukayama M, Masumura M, Hayashi S (1978) Isolation of Kaempferol-3-O-rhamnoglucoside, a Flavonoid Glycoside from *Zephyranthes Candida*. *Zeitschrift für Naturforschung C* 33:587–588
55. Yang CX, Feng BS (2022) Identification of Volatile Components of Flowers Of *Zephyranthes Candida* (Lindl.) Herb. *Bangladesh J Bot* 51:175–178
56. Wei G, Xu Y, Xu M, Shi X, Wang J, Feng L (2024) Identification of Volatile Compounds and Terpene Synthase (TPS) Genes Reveals ZcTPS02 Involved in  $\beta$ -Ocimene Biosynthesis in *Zephyranthes candida*. *Genes (Basel)* 15:185
57. Wu Z, Chen Y, Xia B, Wang M, Dong Y, Feng X (2009) Two Novel Ceramides with a Phytosphingolipid and a Tertiary Amide Structure from *Zephyranthes candida*. *Lipids* 44:63–70
58. Wu Z, Chen Y, Feng X, Xia B, Wang M, Dong Y (2010) Another two novel ceramides from *Zephyranthes candida*. *Chem Nat Compd* 46:187–191

59. Tapia-Campos E, Jose •, Rodriguez-Dominguez M, María De Los •, Revuelta-Arreola M, Van Tuyt JM, Barba-Gonzalez R Floriculture and Ornamental Biotechnology Mexican Geophytes II. The Genera *Hymenocallis*, *Sprekelia* and *Zephyranthes*.
60. Katoch D, Kumar D, Padwad YS, Singh B, Sharma U (2020) Narciclasine-4- O -  $\beta$  -D-xylopyranoside, a new narciclasine glycoside from *Zephyranthes minuta*. *Nat Prod Res* 34:233–240
61. Zhan G, Gao B, Zhou J, Liu T, Zheng G, Jin Z, Yao G (2023) Structurally diverse alkaloids with nine frameworks from *Zephyranthes candida* and their acetylcholinesterase inhibitory and anti-inflammatory activities. *Phytochemistry* 207:113564
62. Moreira NC dos S, Lima JEB de F, Marchiori MF, Carvalho I, Sakamoto-Hojo ET (2022) Neuroprotective Effects of Cholinesterase Inhibitors: Current Scenario in Therapies for Alzheimer’s Disease and Future Perspectives. *J Alzheimers Dis Rep* 6:177–193
63. Cortes N, Posada-Duque RA, Alvarez R, Alzate F, Berkov S, Cardona-Gómez GP, Osorio E (2015) Neuroprotective activity and acetylcholinesterase inhibition of five Amaryllidaceae species: A comparative study. *Life Sci* 122:42–50
64. Zhan G, Zhou J, Liu J, Huang J, Zhang H, Liu R, Yao G (2017) Acetylcholinesterase Inhibitory Alkaloids from the Whole Plants of *Zephyranthes carinata*. *J Nat Prod* 80:2462–2471
65. Zhan G, Liu J, Zhou J, Sun B, Aisa HA, Yao G (2017) Amaryllidaceae alkaloids with new framework types from *Zephyranthes candida* as potent acetylcholinesterase inhibitors. *Eur J Med Chem* 127:771–780
66. Viladomat F, Llabrés JM, Bastida J, Cusidó RM, Codina C (1986) Ontogenic variations in the alkaloids of *Narcissus assoanus*. *Physiol Plant* 68:657–661
67. Zhan G, Zhou J, Liu R, et al (2016) Galanthamine, Plicamine, and Secoplicamine Alkaloids from *Zephyranthes candida* and Their Anti-acetylcholinesterase and Anti-inflammatory Activities. *J Nat Prod* 79:760–766
68. Centeno-Betanzos LY, Reyes-Chilpa R, Pigni NB, Jankowski CK, Torras-Claveria L, Bastida J (2021) Plants of the ‘Libellus de Medicinalibus Indorum Herbis’ from Mexico, 1552. *Zephyranthes fosteri* (Amaryllidaceae) Alkaloids. *Chem Biodivers*. <https://doi.org/10.1002/cbdv.202000834>
69. Shawky E, El Sohafy SM, de Andrade JP, de Souza Borges W (2021) Profiling of acetylcholinesterase inhibitory alkaloids from some *Crinum*, *Habranthus* and *Zephyranthes* species by GC–MS combined with multivariate analyses and in silico studies. *Nat Prod Res* 35:807–814
70. Reyes-Chilpa R, Berkov S, Hernández-Ortega S, Jankowski CK, Arseneau S, Clotet-Codina I, Esté JA, Codina C, Viladomat F, Bastida J (2011) Acetylcholinesterase-inhibiting Alkaloids from *Zephyranthes concolor*. *Molecules* 16:9520–9533
71. Cahlíková L, Kulhánková A, Urbanová K, Valterová I, Macáková K, Kunes J (2010) Analysis of Amaryllidaceae alkaloids from *Zephyranthes robusta* by GC-MS and their cholinesterase activity. *Nat Prod Commun* 5:1201–4
72. Maheshwaran G, Nivedhitha Bharathi A, Malai Selvi M, Krishna Kumar M, Mohan Kumar R, Sudhakar S (2020) Green synthesis of Silver oxide nanoparticles using *Zephyranthes Rosea* flower extract and evaluation of biological activities. *J Environ Chem Eng* 8:104137
73. Rehman MHU, Saleem U, Ahmad B, Rashid M (2022) Phytochemical and toxicological evaluation of *Zephyranthes citrina*. *Front Pharmacol*. <https://doi.org/10.3389/fphar.2022.1007310>
74. Castañeda C, Bravo K, Cortés N, Bedoya J, de Borges WS, Bastida J, Osorio E (2023) Amaryllidaceae alkaloids in skin cancer management: Photoprotective effect on human keratinocytes and anti-proliferative activity in melanoma cells. *J Appl Biomed* 21:36–47
75. Cortes N, Sabogal-Guaqueta AM, Cardona-Gomez GP, Osorio E (2019) Neuroprotection and improvement of the histopathological and behavioral impairments in a murine Alzheimer’s model treated with *Zephyranthes carinata* alkaloids. *Biomedicine & Pharmacotherapy* 110:482–492
76. Chen Z-R, Huang J-B, Yang S-L, Hong F-F (2022) Role of Cholinergic Signaling in Alzheimer’s Disease. *Molecules* 27:1816
77. Hampel H, Mesulam M-M, Cuello AC, Khachaturian AS, Vergallo A, Farlow MR, Snyder PJ, Giacobini E, Khachaturian ZS (2018) revisiting the cholinergic hypothesis in alzheimer’s disease: emerging evidence from translational and clinical research. *J Prev Alzheimers Dis* 1–14
78. Kabir MdT, Uddin MdS, Begum MstM, Thangapandian S, Rahman MdS, Aleya L, Mathew B, Ahmed M, Barreto GE, Ashraf GMd (2019) Cholinesterase Inhibitors for Alzheimer’s Disease: Multitargeting Strategy Based on Anti-Alzheimer’s Drugs Repositioning. *Curr Pharm Des* 25:3519–3535
79. Ago Y, Koda K, Takuma K, Matsuda T (2011) Pharmacological Aspects of the Acetylcholinesterase Inhibitor Galantamine. *J Pharmacol Sci* 116:6–17
80. Cahlíková L, Vrabec R, Pidaný F, Peřinová R, Maafi N, Mamun A Al, Ritomská A, Wijaya V, Blunden G (2021) Recent Progress on Biological Activity of Amaryllidaceae and Further Isoquinoline Alkaloids in Connection with Alzheimer’s Disease. *Molecules* 26:5240
81. He M, Qu C, Gao O, Hu X, Hong X (2015) Biological and pharmacological activities of amaryllidaceae alkaloids. *RSC Adv* 5:16562–16574
82. Elgorashi E, Stafford G, Staden J (2004) Acetylcholinesterase Enzyme Inhibitory Effects of Amaryllidaceae Alkaloids. *Planta Med* 70:260–262
83. Samochocki M, Zerlin M, Jostock R, Groot Kormelink PJ, Luyten WHML, Albuquerque EX, Maelicke A (2000) Galantamine is an allosterically potentiating ligand of the human  $\alpha 4/\beta 2$  nAChR. *Acta Neurol Scand* 102:68–73

84. Kowal NM, Ahring PK, Liao VWY, Indurti DC, Harvey BS, O'Connor SM, Chebib M, Olafsdottir ES, Balle T (2018) Galantamine is not a positive allosteric modulator of human  $\alpha 4\beta 2$  or  $\alpha 7$  nicotinic acetylcholine receptors. *Br J Pharmacol* 175:2911–2925
85. Argade MD, DeCristofano L, Bhattarai N, Schulte MK, Dukat M (2022) Evaluation of galantamine and deconstructed analogs as  $\alpha 7$  nAChR and AChE ligands. *Results Chem* 4:100286
86. Dorronsoro I, Alonso D, Castro A, del Monte M, García-Palomero E, Martínez A (2005) Synthesis and Biological Evaluation of Tacrine-Thiadiazolidinone Hybrids as Dual Acetylcholinesterase Inhibitors. *Arch Pharm (Weinheim)* 338:18–23
87. Moreira NC dos S, Lima JEB de F, Marchiori MF, Carvalho I, Sakamoto-Hojo ET (2022) Neuroprotective Effects of Cholinesterase Inhibitors: Current Scenario in Therapies for Alzheimer's Disease and Future Perspectives. *J Alzheimers Dis Rep* 6:177–193
88. Arias E, Alés E, Gabilan NH, Cano-Abad MF, Villarroya M, García AG, López MG (2004) Galantamine prevents apoptosis induced by  $\beta$ -amyloid and thapsigargin: involvement of nicotinic acetylcholine receptors. *Neuropharmacology* 46:103–114
89. Arias E, Gallego-Sandín S, Villarroya M, García AG, López MG (2005) Unequal Neuroprotection Afforded by the Acetylcholinesterase Inhibitors Galantamine, Donepezil, and Rivastigmine in SH-SY5Y Neuroblastoma Cells: Role of Nicotinic Receptors. *Journal of Pharmacology and Experimental Therapeutics* 315:1346–1353
90. Benfante R, Di Lascio S, Cardani S, Fornasari D (2021) Acetylcholinesterase inhibitors targeting the cholinergic anti-inflammatory pathway: a new therapeutic perspective in aging-related disorders. *Aging Clin Exp Res* 33:823–834
91. Lin M-W, Chen Y-H, Yang H-B, Lin CC, Hung S-Y (2020) Galantamine Inhibits  $A\beta 1-42$ -Induced Neurotoxicity by Enhancing  $\alpha 7$ nAChR Expression as a Cargo Carrier for LC3 Binding and  $A\beta 1-42$  Engulfment During Autophagic Degradation. *Neurotherapeutics* 17:676–689
92. Bhattacharya S, Haertel C, Maelicke A, Montag D (2014) Galantamine Slows Down Plaque Formation and Behavioral Decline in the 5XFAD Mouse Model of Alzheimer's Disease. *PLoS One* 9:e89454
93. EZOULIN M (2008) Antioxidative properties of galantamine on neuronal damage induced by hydrogen peroxide in SK-N-SH cells. *Neurotoxicology* 29:270–277
94. Kita Y, Ago Y, Higashino K, Asada K, Takano E, Takuma K, Matsuda T (2014) Galantamine promotes adult hippocampal neurogenesis via M1 muscarinic and  $\alpha 7$  nicotinic receptors in mice. *Int J Neuropsychopharmacol* 17:1957–1968
95. Alkreathy HM, Esmat A (2022) Lycorine Ameliorates Thioacetamide-Induced Hepatic Fibrosis in Rats: Emphasis on Antioxidant, Anti-Inflammatory, and STAT3 Inhibition Effects. *Pharmaceuticals* 15:369
96. Ilavenil S, Kaleeswaran B, Sumitha P, Tamilvendan D, Ravikumar S (2011) Protection of human erythrocyte using *Crinum asiaticum* extract and lycorine from oxidative damage induced by 2-amidinopropane. *Saudi J Biol Sci* 18:181–187
97. Ilavenil S, Karthik D, Arasu MV, Vijayakumar M, Srigopalram S, Arokiyaraj S, Ravikumar S, Choi KC (2015) Hepatoprotective mechanism of lycorine against carbon tetrachloride induced toxicity in swiss albino mice – A proteomic approach. *Asian Pacific Journal of Reproduction* 4:123–128
98. Ge X, Meng X, Fei D, Kang K, Wang Q, Zhao M (2020) Lycorine attenuates lipopolysaccharide-induced acute lung injury through the HMGB1/TLRs/NF- $\kappa$ B pathway. *3 Biotech* 10:369
99. Park JB (2014) Synthesis and characterization of norbelladine, a precursor of Amaryllidaceae alkaloid, as an anti-inflammatory/anti-COX compound. *Bioorg Med Chem Lett* 24:5381–5384
100. Wang Y-H, Wan Q-L, Gu C-D, Luo H-R, Long C-L (2012) Synthesis and biological evaluation of lycorine derivatives as dual inhibitors of human acetylcholinesterase and butyrylcholinesterase. *Chem Cent J* 6:96
101. McNulty J, Nair JJ, Little JRL, Brennan JD, Bastida J (2010) Structure–activity studies on acetylcholinesterase inhibition in the lycorine series of Amaryllidaceae alkaloids. *Bioorg Med Chem Lett* 20:5290–5294
102. López S, Bastida J, Viladomat F, Codina C (2002) Acetylcholinesterase inhibitory activity of some Amaryllidaceae alkaloids and *Narcissus* extracts. *Life Sci* 71:2521–2529
103. Huang L, Su T, Li X (2013) Natural Products as Sources of New Lead Compounds for the Treatment of Alzheimer's Disease. *Curr Top Med Chem* 13:1864–1878
104. Zhu Q, Zhuang X, Chen J, Yuan N, Chen Y, Cai C, Tan J, Su H, Lu J (2021) Lycorine, a natural alkaloid, promotes the degradation of alpha-synuclein via PKA-mediated UPS activation in transgenic Parkinson's disease models. *Phytomedicine* 87:153578
105. Kang J, Zhang Y, Cao X, Fan J, Li G, Wang Q, Diao Y, Zhao Z, Luo L, Yin Z (2012) Lycorine inhibits lipopolysaccharide-induced iNOS and COX-2 up-regulation in RAW264.7 cells through suppressing P38 and STATs activation and increases the survival rate of mice after LPS challenge. *Int Immunopharmacol* 12:249–256
106. Zhang W, Yang J, Chen Y, Xue R, Mao Z, Lu W, Jiang Y (2021) Lycorine hydrochloride suppresses stress-induced premature cellular senescence by stabilizing the genome of human cells. *Aging Cell*. <https://doi.org/10.1111/ace.13307>
107. Kohelová E, Peřinová R, Maafi N, et al (2019) Derivatives of the  $\beta$ -Crinane Amaryllidaceae Alkaloid Haemanthamine as Multi-Target Directed Ligands for Alzheimer's Disease. *Molecules* 24:1307
108. Peřinová R, Maafi N, Korábečný J, et al (2020) Functionalized aromatic esters of the Amaryllidaceae alkaloid haemanthamine and their in vitro and in silico biological activity connected to Alzheimer's disease. *Bioorg Chem* 100:103928

109. Moraga-Nicolás F, Iturriaga-Vásquez P, Mutis A, Hormazábal E, Bermúdez-Díaz I (2019) Galanthamine and other Amaryllidaceae related alkaloids are inhibitors of  $\alpha 7$ ,  $\alpha 4\beta 2$  and  $\alpha 3\beta 4$  nicotinic acetylcholine receptors. *Revista Brasileira de Farmacognosia* 29:495–499
110. *Phytotherapy Research | Medicinal Chemistry Journal | Wiley Online Library*. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/%28SICI%291099-1573%28199805%2912%3A3%3C205%3A%3AAID-PTR203%3E3.0.CO%3B2-7>. Accessed 8 Feb 2024
111. Castañeda C, Bravo K, Cortés N, Bedoya J, de Borges WS, Bastida J, Osorio E (2023) Amaryllidaceae alkaloids in skin cancer management: Photoprotective effect on human keratinocytes and anti-proliferative activity in melanoma cells. *J Appl Biomed* 21:36–47
112. Tian Y, Wang J, Qin X, Li S, Lan C, Sun X (2022) Narciclasine ameliorated T cell mediated acute liver injury through activating AMPK pathway. *Cell Immunol* 382:104631
113. Zhao D, Zhang LJ, Huang TQ, Kim J, Gu M-Y, Yang HO (2021) Narciclasine inhibits LPS-induced neuroinflammation by modulating the Akt/IKK/NF- $\kappa$ B and JNK signaling pathways. *Phytomedicine* 85:153540
114. Duan Q, Jia Y, Qin Y, Jin Y, Hu H, Chen J (2020) Narciclasine attenuates LPS-induced acute lung injury in neonatal rats through suppressing inflammation and oxidative stress. *Bioengineered* 11:801–810
115. Kim J, Park Y, Chun YS, Cha JW, Kwon HC, Oh MS, Chung S, Yang HO (2015) Effect of *Lycoris chejuensis* and Its Active Components on Experimental Models of Alzheimer's Disease. *J Agric Food Chem* 63:6979–6988