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Original Article

Pharmacological and toxicological effects of Amaryllidaceae

Efeitos farmacológicos e toxicológicos das Amaryllidaceae

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Abstract

The Amaryllidaceae family is widely distributed in the tropics, presenting biological activity attributed mostly to alkaloids, such as an important inhibitory activity of acetylcholinesterase (AChE), antifungal, antibacterial, and cytotoxic activities. The present study aims to review the spectrum of action of the main biological activities and toxicity of secondary metabolites found in Amaryllidaceae through a literature review, using Prisma and the descriptors "Pharmacological effects of Amaryllidaceae" and "Amaryllidaceae family" and "Pharmacological actions of Amaryllidaceae", used in English and Portuguese. The literature search was done in March and May 2023. Original works published from 2012 to 2023, available in full, and presenting experimental and clinical studies were included. After the selection considering the inclusion and exclusion criteria, 60 articles fulfilled the defined criteria. From a pharmacological point of view, the highlight is due to the alkaloid galantamine, which has the potential- and is already used - for treating Alzheimer's. The toxicological aspect must be considered and evaluated carefully, as alkaloids have been associated with adverse effects such as nausea, vomiting, diarrhea, abdominal pain, and cardiovascular, neurological, and respiratory changes. Furthermore, some studies indicate that consuming these plants in significant quantities can lead to hepatic and renal toxicity. Therefore, the therapeutical use of this family's plant drugs and derivatives requires further studies to elucidate its effects and point out metabolites with therapeutic potential.

Keywords: Amaryllidaceae, acetylcholinesterase, alkaloids, pharmacology, toxicology.

Resumo

A família Amaryllidaceae é amplamente distribuída nos trópicos, apresentando atividade biológica atribuída principalmente a alcaloides, com importante atividade inibitória da acetilcolinesterase (AChE), atividade antifúngica, antibacteriana e citotóxica. O presente estudo tem como objetivo revisar o espectro de ação das principais atividades biológicas e toxicidade dos metabólitos secundários encontrados em Amaryllidaceae por meio de uma revisão de literatura, utilizando Prisma e os descritores "Efeitos farmacológicos de Amaryllidaceae" e "Família Amaryllidaceae" e "Ações farmacológicas de Amaryllidaceae ", usado em inglês e português. A busca na literatura foi realizada nos meses de março e maio de 2023. Foram incluídos estudos originais publicados no período de 2012 a 2023, disponíveis na íntegra e apresentando estudos experimentais e clínicos. Após a seleção considerando os critérios de inclusão e exclusão, 60 artigos atenderam aos critérios definidos. Do ponto de vista farmacológico, o destaque fica por conta do alcaloide galantamina, que tem potencial - e já é utilizado - para o tratamento do Alzheimer. O aspecto toxicológico deve ser considerado e avaliado com cautela, pois os alcaloides têm sido associados a efeitos adversos como náuseas, vômitos, diarreia, dor abdominal, alterações cardiovasculares, neurológicas e respiratórias. Além disso, alguns estudos indicam que consumir essas plantas em quantidades significativas pode levar a toxicidade hepática e renal. Portanto, o uso terapêutico de drogas vegetais e derivados desta família requer mais estudos para elucidar seus efeitos e apontar metabólitos com potencial terapêutico.

Palavras-chave: Amaryllidaceae, acetilcolinesterase, alcaloides, farmacologia, toxicologia.

1. Introduction

The Amaryllidaceae family, representing approximately 80 genera and 1600 species (Scobeyeva et al., 2021), is widely distributed worldwide, mainly throughout the tropical and warm regions of the world, such as Brazil, Argentina, Mexico, Sudan, and Senegal. This family is known for its unique alkaloid constituents called Amaryllidaceae alkaloids (AA), with a wide range of biological activities, including acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibition, as well as antitumor, antifungal, antibacterial, antiviral, and antimalarial properties (Havelek et al., 2017; Tallini et al., 2021b). A study by Voss and Kuriakose (2014) revealed that *Hippeastrum puniceum* (Lam.) Kuntze has been traditionally used to cure tumors, hemorrhoids, asthma, and various inflammatory disorders.

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Examples of Amaryllidaceae alkaloids of scientific importance include lycorine (1), galanthamine (2), homolycorine (3), and narcyclasine (4) (Figure 1). Galanthamine is the most prominent alkaloid due to its potent acetylcholinesterase inhibition. It has been recognized and regulated in the pharmaceutical market since 2001 (Maříková et al., 2021), indicated for the palliative treatment of Alzheimer's disease, to manage Alzheimer 'symptoms. Galanthamine's pharmacological action is based on the ability to potentiate cholinergic transmission through a positive allosteric modulation of presynaptic nicotinic receptors (Desgagné-Penix, 2021).

In 2021, the global Dementia Drug market was valued at over USD 13 billion and is estimated to reach USD 28 billion in 2028, with a compound annual growth rate (CAGR) of 8.32%. The role of cholinesterase inhibitors – such galanthamine – in this market, is relevant. Considering only one brand of galanthamine hydrobromide, the global market is expected to reach USD 4.8 billion in 2028, with a CAGR of 3% (2021-2028). This market's increase is partly due to the worldwide population aging. Although half of the global human population is under 30 years old, the United Nations (UN) projections showed that the number of people over 65 will rise from 10% (2023) to 16% in 2050 (Population Matters, 2023). Furthermore, it is estimated that, in the USA, about 6.2 million people aged 65 and above are suffering from Alzheimer's disease. The number of patients is expected to achieve 13.8 billion in 2060 (Grand View Research, 2023).

Therefore, searching for new drugs is imperative, and other Amaryllidaceae alkaloids can be a potential alternative to galanthamine. However, the screening and the large-scale production of Amaryllidaceae alkaloids pose several challenges. For example, many alkaloids in the Amaryllidaceae family exist in small amounts, and methods for isolating and purifying them are generally inefficient and environmentally unsustainable (Zaragoza-Puchol et al., 2021). Hence, it is important to highlight that Amaryllidaceae species are not abundant, and mining and agriculture activities and urban growth are reducing plant populations in this family. Thus, it is essential to develop sustainable propagation methods for the domestication of Amaryllidaceae, such as mass distribution of seeds, bulb division, and micro aggregation (Zaragoza-Puchol et al., 2021). Chemical synthesis can help alleviate the demand for limited Amaryllidaceae alkaloids. However, producing these complex molecules is often challenging and expensive, although some specialized synthetic methods have been developed that can be used to build several intermediate pathways (Jin, 2009; Gasca et al., 2020).

Moreover, despite their interesting medicinal characteristics, Amaryllidaceae plants are known to cause poisoning, and several of them have been classified as such, drawing attention to cases of toxicity (Havelek et al., 2017). Therefore, attention has been drawn to plants in this family used in medicine and traditional practice due to their toxic properties, putting the health of communities worldwide at risk (Nair and Van Staden, 2013). And investigations to assess its safety and studies evaluating its pharmacological and therapeutic activities are necessary.

Considering the importance of Amaryllidaceae and galanthamine, this study aimed to evaluate the Amaryllidaceae pharmacological and toxicological state-of-art.

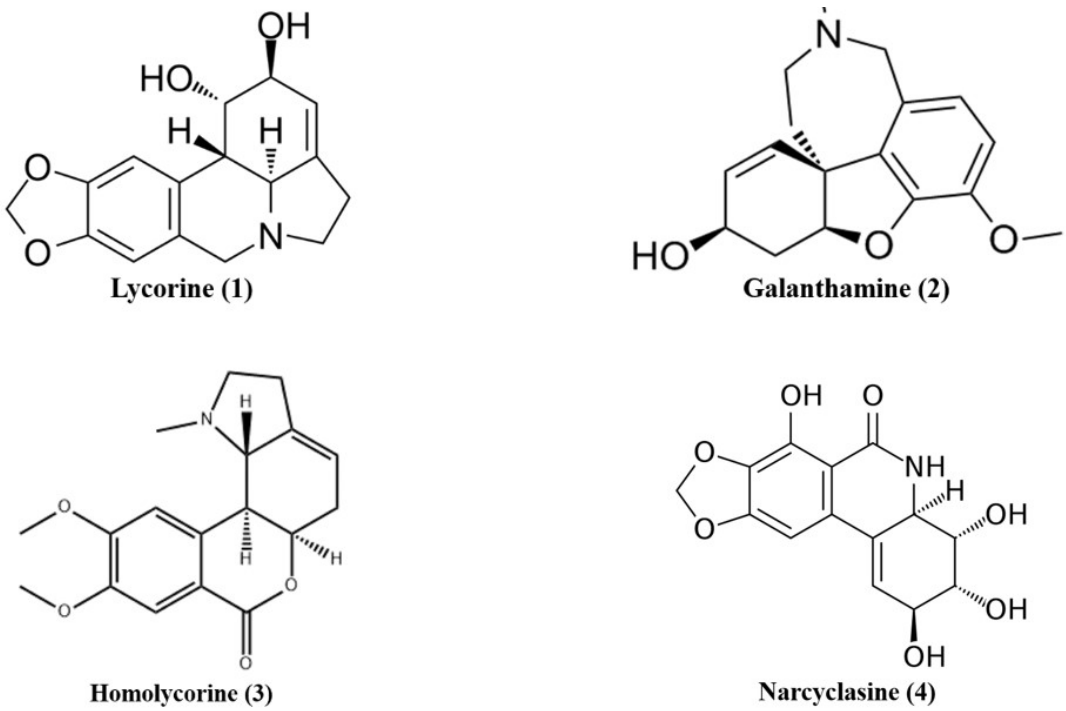

Figure 1. Examples of chemical constituents in the plant family Amaryllidaceae.

2. Material and Methods

This study was a systematic literature review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (Figure 2). We formulated the question focusing on the pharmacological activity of the Amaryllidaceae plants. The searched databases were PubMed, MEDLINE, Periodicos Capes via CaFe and SciELO, using keywords obtained by consulting the Health Sciences Descriptors (DeCS) according to the particularities of each database: "Pharmacological effects of Amaryllidaceae" AND "Family Amaryllidaceae" AND "Amaryllidaceae pharmacological actions" in English and Portuguese. The search was conducted between March and May 2023, according to the following criteria: original works published in 2012-2023 and available as full text; those using experimental and clinical studies as methodology were included. Reviews, studies that evaluated traditional and folk knowledge, papers published in congresses, or presentations were excluded. Moreover, the World Flora Online (WFO, 2023) and Reflora (JBRJ, 2023) databases were consulted to verify any changes in the botanical name of the plant species, and the accepted name was considered.

3. Results and Discussion

The search strategy resulted in 361 studies published from January 2012 to May 2023, and the articles were available in the analyzed databases according to the predefined descriptors. Of these, 49 articles were found in PubMed, 15 in MEDLINE, 265 through Periódicos Capes via CaFe, and 32 in SciELO. The inclusion and exclusion criteria were applied, and duplicates were eliminated, resulting in 60 articles selected for this review (Table 1).

After analyzing the results, *in vivo* and *in vitro* studies were the most reported research. The prominent finding was the effect of Amaryllidaceae plants in inhibiting the enzyme acetylcholinesterase, as shown in Table 1.

3.1. Pharmacology

The cholinergic system depends on normal acetylcholine (ACh) levels, a neurotransmitter involved in learning and memory. This neurotransmitter is found in the brain and at neuromuscular junctions, and acetylcholine hydrolysis is essential for synaptic cholinergic transmissions before new electrical impulses (Sobiecki, 2002). This process is carried out by the enzyme AChE, which mediates synapses in the nervous system (Nair and Van Staden, 2022). Inhibition of acetylcholinesterase activity is one of the most notable effects of alkaloids from a wide range of different species of Amaryllidaceae (Maroyi, 2016). Among AChE inhibitors, galanthamine, a natural product used to treat Alzheimer's disease, possesses selective, prolonged, and reversible action, with the ability to improve performance in memory tests (Marco and do Carmo Carreiras, 2006; Cahlíková et al., 2021).

Galanthamine was the first alkaloid obtained from the bulbous plant *Galanthus woronowii* Losinsk., native to northeast Turkey, and has been used since 2001 for palliative therapy in mild to moderate Alzheimer's disease. This discovery encouraged searching for and isolating other active substances in different Amaryllidaceae plants.

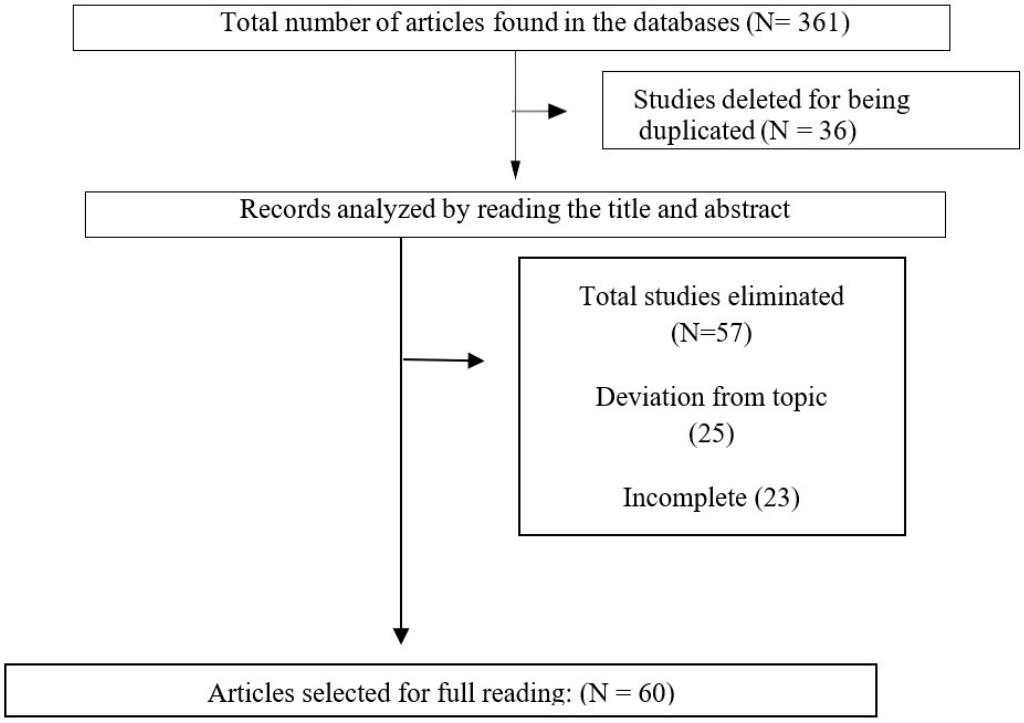

Figure 2. Summary of the method used to include studies on the pharmacology and toxicology of the Amaryllidaceae family.

Table 1. Distribution of articles selected for the systematic review.

Reference	Main Topic	Plants	Conclusions
Havelek et al. (2017)	The anticancer potential of Amaryllidaceae alkaloids was assessed by screening with a panel of human cells, real-time cell analysis, and Ehrlich tumor-bearing mice.	*Zephyranthes robusta* (Herb.ex Sweet) Baker; *Chlidanthus fragrans* Herb; *Nerine bowdenii* W.Watson*; Narcissus poeticus* L.	Hemantamine and lycorine can inhibit cell proliferation of 16 human cancer cell lines from different tissue origins.
Aziz et al. (2014)	The anthelmintic activity of *Crinum latifolium* leaves was assessed on *Pheritima posthuma*. Cytotoxicity was evaluated using the brine shrimp model.	*Crinum latifolium* L.	The crude methanol extract from leaves presented a mild anthelmintic activity compared to albendazol and low toxicity to *Artemia salina*
Tijani et al. (2012)	Evaluate the wound healing activity of an ointment containing *Crinum zeylanicum* bulbs extract	*Crinum zeylanicum* (L.) L.	The ointment did not present acute dermal toxicity and promoted wound retraction and epithelization in rats, accelerating the healing process.
Masi et al. (2019)	Non-alkaloid compounds from *Crinum biflorum* bulbs were tested for cytotoxicity	*Crinum biflorum* Rottb.	Flavonoids and coumarine derivatives were tested against HeLa and A431 cancer cell lines and were active. *N-p*-coumaroyltyramine was toxic to cancer cells and protected HaCat cells against oxidative stress. The flavonoid derivatives presented AChE inibition activity and the coumarin derivative presented α-amylase and β-glucosidase inhibition.
Omoruyi et al. (2021b)	The potential *in vitro* neuroprotection, antioxidant activities and cytotoxicity of *Crossyne flava* extract and isolated alkaloids	*Crossyne flava* (W.F.Baker ex Snijman) D.Müll.-Doblies & U.Müll.-Doblies	The crude extract of bulbs,pancratinine B, buphanidrine, and buphanisine did not interfere in the SH-SY5Y cells viability; epibuphanisine was cytotoxic in high concentration. The extract and all compounds presented neuroprotection by attenuating ATP levels in the cells and inhibited MPP^+-induced apoptosis
Tayoub et al. (2018)	Anti-proliferative effects of *Pancratium maritimum* extracts on MDA-MB-321 cells	*Pancratium maritimum* L	Extracts from bulbs and leaves of *Pancratium maritimum* inhibit MDA-MB-321 cell proliferation, through cell arrest at S and G_2/M phases. The extracts also affected Cyclin B1, Bcl-2, and Ki67 expression
Berkov et al. (2021)	The alkaloid-rich (without lycorine) fraction of *Narcissus* cv. Hawera showed *in vitro* AchE inhibition, cytotoxic activities, and *in vivo* anxiolytic and anti-depressant-like activities in mice.	*Narcissus* cv. Hawera	The alkaloid-rich fraction anxiolytic effect is sex-dependent and was observed only in male mice, while female mice did not change their anxiety-like behavior after treatment. In the anti-depressant-like assay, female mice were more sensitive to the alkaloid-rich fraction than male mice. Male mice needed a higher dose than used for female mice to decrease the immobility time. The alkaloid-rich fraction inhibited HL-60 and BV-173 cell lines growth, but only a highest dose was able to inhibit MDA-MB-231 cell.
Ka et al. (2021)	Evaluate the antivirus activity of an alkaloid extract of *Crinum jagus*	*Crinum jagus* (J.Thomps) Dandy,	*Crinum jagus* alkaloid extract and cherilline presented antiviral activity against DENV, ZIKV, but were inactive against HIV-1.

*Synonim not found at WorldFloraOnline. Abbreviations: AChE, acetylcholinesterase; BuChE, butyrylcholinesterase.

Table 1. Continued...

Reference	Main Topic	Plants	Conclusions
Cole et al. (2019)	The cytotoxicity of alkaloids from two Amaryllidaceae species was evaluated	*Griffinia gardneriana* (Herb.) Ravenna; *Zephyranthes cearensis* (Herb.) Baker	11-hydroxyvittatine and 2-α-7-dimethoxyhomolycorine were not toxic to tested cell lines (L929, HepG2, MCF-7, A549). Tazzetine, trisphaeridine, and sanguinine showed activity on fibroblast lineage (L929). Lycorine and pretazettine were 10 to 30 folds more cytotoxic than the other alkaloids to all cell lines, presented genotoxicity, and promoted apoptosis via the caspase-3 pathway.
Tegegne et al. (2022)	The anti-diabetes and anti-hyperlipidemic activities of *Crinum abyssinicum* extract were tested in mice	*Crinum abyssinicum* Hochst. ex A. Rich	A hydro-alcoholic extract of *Crinum abyssinicum* shoot tips presented anti-hyperglycemic, anti-hyperlipidemic, and body weight improvements in streptozotocin-induced diabetic mice. Moreover, it showed hypoglycaemic and anti-hyperglycaemic activities in normoglycemic and oral glucose-loaded mice, respectively, corroborating the traditional use of this plant as an antidiabetic remedy.
Benedec et al. (2018)	Four Amaryllidaceae species were evaluated for antioxidant and antimicrobial activities.	*Galanthus nivalis* L., *Narcissus pseudonarcissus* L., *N. poeticus* L., *Leucojum vernum* L.	The hydroetanolic extracts of aerial parts were tested against *Salmonella typhimurium, Escherichia coli, Listeria monocytogenes, Staphylococcus aureus, Candida albicans,* and *Aspergillus brasiliensis*. Concerning the five antioxidant assays, only G. *nivalis* extract showed activity. *Galanthus nivalis* and *L. vernum* inhibited *S. aureus* growth, and *N. poeticus* presented antifungal activity.
Eriksson et al. (2012)	Amaryllidaceae alkaloids were evaluated for P-glycoprotein interaction	Some tested alkaloids were isolated from *Crinum bulbispermum* (Burm.f.) Milne-Redh. & Schweik, *C. moorei* Hook.f., and *Cyrtanthus falcatus* R.A.Dyer	Nine Amaryllidaceae alkaloids were tested on P-gp mediated calcein-AM efflux. Epibuphanisine, papyramine and lycorine did not interact with P-gp. Galanthamine showed weak interaction. Crinine, 6-hydroxycrinamine, powelline, 3-*O*-acetylhamayne and 1-epi-deacetylbowdenisine showed interaction with P-gp. It was observed that there was no structure-activity relationship.
Masi et al. (2019)	Alkaloids from *Haemanthus humilis* bulbs were tested for cytotoxicity	*Haemanthus humilis* Jacq.	Montanine inhibit the growth of all tested cell lines (A549, HCT-15, SK-MEL-28, MCF7, MDA-MB-231, Hs578T); coccinine also was active except in SK-MEL-28. Incartine and albomaculine did not present activity.
Onishi et al. (2012)	Lycorine and lycoricidinol (narciclasine) were evaluated for possible interference in the circadian period using a real-time reporter gene assay system based on NIH3T3 cells.	*Lycoris radiata* (L'Hérb.) Herb.	Both alkaloids promoted the elongation of the circadian period in a reversible way. Authors suggested that lycorine and lycoricidinol modulate Bmal1 transcription and the circadian period, and Lycoris alkaloids can contribute to the control of period length in mammalian cells.

*Synonim not found at WorldFloraOnline. Abbreviations: AChE, acetylcholinesterase; BuChE, butyrylcholinesterase.

Table 1. Continued...

Reference	Main Topic	Plants	Conclusions
Doskočil et al. (2015)	Alkaloids from two Amaryllidaceae species were evaluated for toxicity to gastrointestinal cancer cells.	*Zephyranthes robusta* (Herb. ex Sweet) Baker, *Chlidanthus fragans* Herb.	Thirteen alkaloids were tested for toxicity to CaCo-2, HT-29, and FHs-74 Int cell strains. Haemanthamine, haemanthidine and lycorine presented toxicity to cancer cells and low toxicity to the normal line (FHs-74).
Cavallaro et al. (2014)	Alkaloids from two Amaryllidaceae plants presenting acetyl- and butyrylcholinesterase-inhibiting activity	*Zephyranthes tubispatha* (L'Hérb) Herb., *Habranthus jamesonii* (Baker) Ravenna	The levels of lycorine and hypeastidine, important AChE inhibitors, observed in *H. tubispathus* bulbs may be responsible for AChE inhibition.
Cortes et al. (2015)	Alkaloid-rich fractions from five Amaryllidaceae species were tested for neuroprotective activity in an *ex-vivo* model (glutamate excitotoxicity in rat cortical neurons)	*Urceolina bonplandii* (Kunth) Traub, *U. caucana* (Meerow) Christenh. & Byng, *Clivia miniata* Regel, *Crinum jagus* (J.Thomps) Dandy, *Phaedranassa lehmannii* Regel, *Hippeastrum elegans* (Spreng.) H.E. Moore	Alkaloid-rich fractions from U. b*onplandii* bulbs, U. *caucana* bulbs, and *C. miniata* leaves, exerted neuroprotective action. Authors, suggested the activity is due to the ability to stabilize the free radicals generated from an excitotoxic process mediated by Glutamate.
Sóto-Vasquez et al. (2022)	Alkaloid-rich fraction was tested for AChE and BUChE inhibition and antiplasmodial against *Plasmodium falciparum* activity *in vitro*	*Ismene amancaes* Herb.	The alkaloid-rich fraction of *I. amancaes* bulbs presented low AChE and BuChE and moderate antiplasmodial activities
Sóto-Vasquez et al. (2021)	Alkaloid-rich fractions of two *Clinanthus* species were tested *in vitro* for antiplasmodial activity against *Plasmodium falciparum*	*Clinanthus incarnatus* (Kunth) Meerow, *C. ruber* (Herb.) Meerow & A.Cano	The alkaloid-rich fractions presented activity against *P. falciparum* Chloroquine-resistant strain
Kaya et al. (2017)	*In vitro* evaluation of AChE and BuChE inhibition and anti-inflammatory activity	*Galanthus cilicicus* Baker	The alkaloid-rich fraction from aerial parts and bulbs of *G.cilicicus* did not affect the viability of HUVEC cells. Both fractions inhibited AChE and BuChE and presented potential anti-inflammatory activity by inhibiting the interaction of leukocytes and endothelial cells
Karakaya et al. (2019)	Anti-oxidant and AChE and BUChE inhibition of extract, fractions and essential oil of *Allium tuncelianum*	*Allium tuncelianum* (Kollmann) Özhatay, B.Mathew & Siraneci	All samples inhibited AChE and BuChE and the ethyl acetate fraction was the most active.
Castillo et al. (2018)	Evaluation of neuroprotetive activity against β–amyloid DNA damage	*Caliphruria subedentata* Baker	Ethanolic extract of *C. subdentata* aerial parts protected SH-SY5Y cells against damage by $A\beta_{(1-42)}$, and reduced the induced mitocondrial morphological changes and cell death. Also, protected SH-SY5Y cells against getonoxic effects and DNA strand breaks induced by $A\beta_{(1-42)}$. Moreover, the extract was not toxic to SH-SY5Y cells and could inhibit AChE.
Chen et al. (2016)	Evaluate the potential Topoisomerase I inhibition	*Lycoris radiata* (L'Hér.) Herb.	An alkaloid-rich fraction of bulbs was able to inhibit topoisomerase I in a dose-dependent way, and hippeastrine seems to be involved in the inhibition. Hippeastrine inhibited the proliferation of HT029 and HepG2 cells.
Napo et al. (2020)	Evaluate three Amaryllidaceae species for citotoxicity to K562 leukaemia cells	*Crinum bulbispermum* (Burm.f.) Milne-Redh. & Schweik., *Boophone disticha* Herb., *Amaryllis belladona* L.	Aqueous and methanol extracts from bulbs of *C. bulbispermum* and *B. disticha* and methanol extract from *A. belladona* roots showed a high inhibition rate of K562 cells.

*Synonim not found at WorldFloraOnline. Abbreviations: AChE, acetylcholinesterase; BuChE, butyrylcholinesterase.

Table 1. Continued...

Reference	Main Topic	Plants	Conclusions
Kianfé et al. (2020)	Anti-microbial activity of extract, fractions and alkaloids from *Crinum glaucum* leaves	*Crinum glaucum* A.Chev.	The ethanol extract, the fractions EtOAC and n-BuOH, and 5,6-dihydrobicolorine, lycorine, and ungeremine presented mild antimicrobial activity against *Enterococcus faecalis* and *Pseudomonas aeruginosa, Proteus mirabilis*. None was active against *Escherichia coli* or *Staphylococcus aureus*
Minkah and Danquah (2021)	Evaluate the *in vitro* antimicrobial and *in vivo* anti-inflammatory activities of *Crinum jagus*	*Crinum jagus* (J.Thomps) Dandy	In rats, he bulbs' aqueous extract presented anti-inflammatory activity and the ethanol extract showed antipyretic activity. The methanol extract inhibited the growth of *Mycobacterium smegmatis, Salmonella typhi* and *Pseudomonas aeruginosa.*
Sikder et al. (2021)	Evaluation of the anti-bacterial, anti-inflammatory, thrombolytic, and anti-diarrheal activities	*Crinum viviparum* (Lam.) R.Ansari & V.J.Nair	The ethanolic extract of *C. viviparum* whole plant a very low activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella enterica*. The extract presented a mild thrombolitic and anti-inflammatory activity *in vitro*. On the other hand, the extract presented antidiarrhoeal activity in mice.
He et al. (2013)	In vitro evaluation of 15 alkaloids against influenza A virus	*Lycoris radiata* (L'Hér.) Herb.	Lycorine, hippeastrine, hemanthamine, and 11-hydroxyvittatine presented post-treatment antiviral activity against H5N1, by blocking vRNP nuclear export. The compounds were not toxic to MDCK cells.
Donald et al. (2018)	Evaluation of the central and peripheral analgesic activity of aqueous and hydroalcoholic extracts from *Crinum scillifolium* bulbs in mice	*Crinum scillifolium* A.Chev.	The hydroethanolic extract exerted a dose-dependent reduction in writhes, comparable to aspirin. The aqueous extract decreased abdominal writhing induced by the acetic acid. On the other hand, the evaluation results of central analgesic activity were inconclusive.
Omoruyi et al. (2021a)	Evaluation of the two Amaryllidaceae species neuroprotective effect in an *in vitro* model	*Clivia miniata* (Lindl.) Bosse, *Nerine humilis* Herb.	The pre-treatment of SH-SY5Y with methanol extract of *C. miniata* or *N.humilis* bulbs improved cell viability and morphology by inhibiting the toxicity and apoptosis induced by MPP*. On the other hand, the extracts showed weak antioxidant activity.
Rahman et al. (2013)	Evaluation of analgesig and anti-inflammatory activi of Crinum asiaticum ethanol extract.	*Crinum asiaticum* L.	The ethanol extract of *C. asiaticum* leaves exerted anti-inflamatory and analgesic effect in mice. In analgesic assay, the extract reduced the pain induced by acetic acid; in carrageenan-induced paw edema, the extract reduced the edema. In the acute toxicity test, no death was observed among the tested animals

*Synonim not found at WorldFloraOnline. Abbreviations: AChE, acetylcholinesterase; BuChE, butyrylcholinesterase.

Table 1. Continued...

Reference	Main Topic	Plants	Conclusions
Ncube et al. (2015)	Sazonal influence on biological activity and alkaloid content	*Cyrtanthus contractus* NE Br.	High alkaloid amounts were observed in high temperature and rainfall period. The cytotoxicity of the ethanol extract of bulbs to CEM, MCF7, HeLa and BJ cell lines varied, depending on the period of the bulbs collection. The extract also was able to inhibit COX-1 and -2, as well as AChE and presented antimicrobial activity against *Bacillus subtilis*, *Klebsiela pneumoniae, Staphulococcus aureus* and *Escherichia coli*, comparable to Neomycin; and anticandida activity comparable to Amphotericin B
Tallini et al. (2021a)	Alkaloid profile and enzyme inhibition by ethanol extracts from bulbs and leaves of *Crinum* x *amabile*	*Crinum* x *amabile* Donn.*	Ethanol extracts from bulbs and leaves inhibited AChE and BuChE in an *in vitro* model.
Silva et al. (2022)	Lycorine and ethanol extracts from bulbs and leaves of *Crinum americanum* with anticandida effects	*Crinum americanum* L	Ethanol extracts from bulbs and leaves of C. americanum presented moderate activity against *Candida auris*, *C. albicans*, *C. krusei* and *C. parapsilosis*.
Isbilen et al. (2018)	*Allium autumnale* bulbs and stem presented low *in vitro* cytotoxic activity	*Allium autumnale* P.H.Davis	The ethanol extracts of bulbs and stems were not toxic to MCF-7 and MDA-MB-231 cells.
Attia et al. (2021)	Mucilage isolated from H*ippeastrum vittatum* bulbs presented hypoglycaemic activity in rats	*Hippeastrum vittatum* (L'Hér.) Herb	Oral administration of the mucilage ameliorated the induced hyperglycaemia in rats
El Samarji et al. (2023)	Evaluate the in vitro anti-proliferative effect of ethanol extract from *Sternbergia clusiana* bulbs.	*Sternbergia clusiana* Ker Gawl. ex Schult.	The extract reduced the viability of MCF-7 and MDA-MB-231 cells, with no effect on normal mesenchymal stem cells. The effect seems to be throught the activation of the apoptotic pathway due to the increase in cellular and DNA fragmentation; alterations in apoptotic proteins (Bax, Bcl-2 and c-PARP); and a decrease in ROS production.
Gomes-Copeland et al. (2022)	Evaluation of ethanol extract from *H. stapfianum* leaves on AChE activity nuclear receptors PPAR-α and PPAR-γ.	*Hippeastrum stapfianum* (Kraenzl.) R.S.Oliveira & Dutilh	The ethanol extract of *H. stapfianum* activated PPAR-α and PPAR-γ, presented mild AChE inhibition and antioxidant activity
Taiwe et al. (2016)	Evaluation of anticonvulsivant activity of *Crinum jagus*	*Crinum jagus* (J.Thomps) Dandy	A flavonoid-rich fraction of an ethyl acetate extract of leaves increased the latency to myoclonic jerks, clonic seizures, and decreased the number of myoclonic jerks in PTZ-kindled mice. Moreover, the fraction did not alter the locomotion of animals in the open-field or rotarod tests, and decreased lipid peroxidation, and augmented endogenous antioxidant enzymes in brain.
Donald et al. (2017a)	Evaluation of anticonvulsivant activity of *Crinum scillifolium*	*Crinum scillifolium* A.Chev.	The aqueous extract of *Crinum scillifolium* bulbs protected mice against seizures induced by isoniazid, increased seizure latency, and reduced the occurrence of death.

*Synonim not found at WorldFloraOnline. Abbreviations: AChE, acetylcholinesterase; BuChE, butyrylcholinesterase.

Table 1. Continued...

Reference	Main Topic	Plants	Conclusions
Donald et al. (2017b)	Evaluation of anticonvulsivant activity of *Crinum scillifolium*	*Crinum scillifolium* A.Chev.	The hydroethanolic extract of *Crinum scillifolium* bulbs protected mice against seizures induced by isoniazid, delayed the convulsion onset, and no mortality was found of the mice against isoniazid-induced convulsion.
Gonring-Salarini et al. (2019)	Evaluation of antiplasmodial activity of *Worsleya procera* roots	*Worsleya procera* (Lem.) Traub	Fractions of methanol extract from W. procera roots presented antiplasmodial activity. The fractions presented low toxicity to HepG2 cells. Among isolated alkaloids, only lycorine presented activity against Plasmodium falciparum 3D7 and K1 strains without reducing the HepG2 cell viability.
Johnson et al. (2018)	Evaluation of cytotoxicity and antioxidant activity of *Pancratium triflorum* whole plant extracts	*Pancratium triflorum* Roxb.	The petroleum ether, acetone, chloroform, and methanol extracts from P.triflorum whole plant were tested for antioxidant potential and were not active. All extracts presented moderate toxicity to *Artemia salina* larvae.
Nasir et al. (2022)	Silver nanoparticules of *Allium sativum* were active against Aedes aegypti	*Allium sativum* L.	Silver nanoparticules containing acetone extract of *A. sativum* bulbs presented larvicidal activity against Aedes aegypti 2nd and 3rd instar larvae
Martinez-Peinado et al. (2022)	Anti-*Trypanosoma cruzi* activity of alkaloids isolated from *Zephyrantes brachyandra*	*Zephyranthes brachyandra* (Baker) Baker	The extract showed specific anti-*T. cruzi* activity; ismine seems to be partially responsible for this. These results encourage the exploration of *Z. brachyandra* alkaloids in search of new starting points for developing drugs for Chagas disease.
Gasca et al. (2020)	Acetylcholinesterase inhibitory activity, anti-inflammatory, and neuroprotective potential of *Hippeastrum psittacinum*	*Hippeastrum psittacinum* Herb.	Ethanol extract and alkaloid fractions from *H. psittacinum* bulbs inhibited AChE. *H. psittacinum* protected SH-SY5Y cells from hydrogen peroxide-induced neurotoxicity.
Hulcova et al. (2019)	Amaryllidaceae alkaloids from *Narcissus pseudonarcissus* as potential drugs in the treatment of Alzheimer's disease	*Narcissus pseudonarcissus* L. cv. Dutch Master	Narcimatulin revealed an interesting multipotent profile exerting inhibition properties for BuChE and AChE enzymes.
Al Mamun et al. (2020)	Amaryllidaceae alkaloids of the belladine type of *Narcissus pseudonarcissus* as new selective butyrylcholinesterase inhibitors	*Narcissus pseudonarcissus* cv. Carlton	Carltonine showed important direct inhibitory action on BuChE and AChE.
Katoch and Sharma (2019)	Simultaneous quantification and identification of Amaryllidaceae Alkaloids in *Narcissus tazetta* by ultra performance liquid chromatography, diode array detector-electrospray ionization tandem mass spectrometry.	*Narcissus tazetta* L.	Leaves and flowers are good sources of alkaloids in addition to bulbs. They can be used to inhibit enzymes capable of causing neurodegenerative diseases.
Al Shammari et al. (2021)	Amaryllidaceae alkaloids from *Hippeastrum* X *hybridum*, and preparation of vittatine derivatives as potential ligands for Alzheimer's disease	*Hippeastrum* X *hybridum* CV. Ferrari	Potential treatment for Alzheimer's disease confirmed, and expectations for developing new pharmaceutical products.

*Synonim not found at WorldFloraOnline. Abbreviations: AChE, acetylcholinesterase; BuChE, butyrylcholinesterase.

Table 1. Continued...

Reference	Main Topic	Plants	Conclusions
Kohelova et al. (2021)	Alkaloids from *Zephyranthes citrina* and their implication in Alzheimer's disease: isolation, structural elucidation and biological activity	*Zephyranthes citrina* Baker	A significant ability to inhibit human AChE and BuChE was detected. This property was demonstrated by alkaloid narcyyline. This compound is also predicted to cross the blood-brain barrier (BBB) through passive diffusion.
Maříková et al. (2021)	Elucidation of the structure and cholinesterase inhibition activity of two new minor alkaloids from Amaryllidaceae	*Hippeastrum hybridum*, *Narcisus pseudonarcissus*	Narcikachnine-type alkaloids possess an interesting structural framework with the potential for cholinesterase inhibition and the production of a new herbal medicine.
Salas Olivet et al. (2020)	Pharmacognostic study of *Hymenocallis caribaea*	*Hymenocallis caribaea* L (Herb)	Suggests the presence of phenols, flavonoids, saponins, and especially alkaloids.
Rojas-Vera et al. (2021)	Alkaloid profile and cholinesterase inhibition activity of five Amaryllidaceae species collected in Mérida,Venezuela	*Crinum amabile* Donn ex Ker Gawl., *C. americanum* L., *C. moorei* Hook.f., *Amaryllis belladonna* L, *Zephyranthes carinata* Herb.	Alkaloid extracts showed a high to a moderate inhibitory effect on AChE and BuChE. The alkaloid bufanisine demonstrated interesting theoretical inhibitory activity against BuChE by molecular docking.
Zaragoza-Puchol et al. (2021)	Analysis of *Habranthus cardenasianus* alkaloids, anti-cholinesterase activity, and biomass production by propagation strategies	*Habranthus cardenasianus* Traub. & I.S.Nelson	The alkaloid analysis of bulbs showed that they are a source of antitumor alkaloids, especially pretazettin (tazettin), and a sustainable strategy for their propagation and domestication for bioactive alkaloid production.
Seoposengwe et al. (2013)	*In vitro* neuroprotective potential of medicinal plants against rotenone-induced toxicity in SH-SY5Y neuroblastoma cells	*Crinum bulbispermum* (Burm.f.) Milne-Redh. & Schweik.	Plant bulb extracts at concentrations as high as 25 µg/mL offered little protection to SH-SY5Y cells pre-exposed to the harmful effects of isoflavone rotenone, being potentially toxic.
Voss and Kuriakose (2014)	Pharmacognostic and phytochemical evaluation of the bulbs of *Hippeastrum puniceum*	*Hippeastrum puniceum* (Lam.) Kuntze	The plant has the potential ability to treat inflammatory diseases, gastrointestinal disorders and cancer.
Adewusi et al. (2012)	Cytotoxicity and acetylcholinesterase inhibitory activity of a crinine alkaloid isolated from *Boophone disticha*	*Boophone disticha* Herb.	The compound 6-hidroxycrinamine was found to be toxic to neuroblastoma cells. Despite the toxicity of crinine-type alkaloids, quantitative studies of the structure-activity relationship can be used to modify the structures to make them less harmful and improve their activity.
Le et al. (2023)	Anti-SARS-CoV-2 Activity and cytotoxicity of Amaryllidaceae Alkaloids from *Hymenocallis littoralis*	*Hymenocallis littoralis* (Jacq.) Salisb.	Assessment of cytotoxicity on the Vero-E6 cell line revealed lycorine and pancratistatin as cytotoxic substances with CC50 values of 1.2 µM and 0.13 µM, respectively. The preliminary structure-activity relationship for the lycorine-type alkaloids in this study was further investigated, and as a result, ring C appears to play a crucial role in their anti-SARS-CoV-2 activity.
Butler and Johnson (2022)	Seed dispersal by monkey spittoon in *Scadoxus* (Amaryllidaceae): fruit selection, dispersal distances, and effects on seed germination	*Scadoxus multiflorus* (Martyn) Raf., *S. puniceus* L. Friis & Nordal	Seeds of *Scadoxus* are unorthodox, supposedly poisonous, and encased in fleshy fruits. The ripe red fruits of *Scadoxus* attract monkeys, who consume the fleshy fruit and spit out the seeds, putting the community at risk.

*Synonim not found at WorldFloraOnline. Abbreviations: AChE, acetylcholinesterase; BuChE, butyrylcholinesterase.

Other Amaryllidaceae alkaloids, such as lycorine and haemantidine, also act as AChE inhibitors, demonstrating their pharmacological potential (Cavallaro et al., 2014). There is, therefore, a great interest in searching for sources of galanthamine (Havelek et al., 2017; Kohelova et al., 2021).

To date, different species have been studied for their alkaloid profile using gas chromatography-mass spectrometry, and several alkaloids of different structural types have been isolated and selected for various biological activities.

The alkaloids from Amaryllidaceae are used to treat degenerative diseases and neurological disorders. In a preclinical study conducted by Cortes et al. (2015), the alkaloid extract from *Crinum jagus,* bulbs at concentrations of 0.3 and 2.9 µg/mL, showed high neuroprotective and inhibitory activity against AChE. In this study, other species of Amaryllidaceae, such as *Crinum bulbispermum,* at concentrations of 0.3 µg/mL and 2.9 µg/mL, *Zephyranthes carinata* (2.9 µg/mL), and *Hippeastrum puniceum* (2.9 µg/mL), exhibited inhibitory activity against AChE, possibly associated with alkaloids of the lycorine and galanthamine types. Lycorine is also associated with improvements in peripheral nerve function and autophagy-associated proteins in diabetic mice, indicating it may be a potential alkaloid for treating diabetic peripheral neuropathy (Yuan et al., 2022).

Montanine has been characterized as behaviorally and toxicologically active. In mice, montanine showed a LD_{50} of 64.7 mg/kg and 67.6 mg/kg for male and female, respectively (Koutova et al., 2020). It has been shown to reduce motor activity and induce sedative, anxiolytic, anticonvulsant, and antidepressant effects in mice at a dose of 10 µL/g of body weight (Silva et al., 2006).

Several studies have reported perspectives on using plants from this family to treat tropical diseases, such as Chagas Disease. Martinez-Peinado et al. (2022) presented an *in vivo* clinical study. A hexane extract from bulbs of *Habranthus brachyandrus* was used, at concentrations of 754 µg/mL of extract and 500 µM. The findings revealed its potential ability to eradicate the main pathogen responsible for the disease. Furthermore, the plant extract showed high specific anti-*Trypanosoma cruzi* activity, and the isolated alkaloid, ismine, was partially responsible for this. These results encourage the exploration of *H. brachyandrus* alkaloids in the search for new drugs for Chagas disease.

In *Boophane disticha,* for example, alkaloids such as buphanidrine, buphanamine, and distichamine-type alkaloids have an affinity for the serotonin transporter, indicating their potential in the treatment of depression and anxiety (Neergaard et al., 2009).

It is worth noting that the search for new drugs for neglected tropical diseases, such as Chagas disease, is of utmost importance to public health. The limited treatment options and the high prevalence of these diseases in resource-limited settings necessitate the development of affordable and accessible therapeutics. Therefore, the exploration of *H. brachyandrus* alkaloids as potential anti-Chagas agents represents a promising avenue for discovering new drugs that could significantly impact global health.

It is important to highlight studies that report the perspective of using plants from this family to assess their ability to combat parasitic worms (helminths) in a laboratory setting. The plant *Crinum latifolium L.* demonstrated anthelmintic activity at doses of 50mg/ml, where the crude extract was able to inhibit the growth and eliminate helminths. In addition to anthelmintic activity, researchers investigated the total phenolic content of the plant. Phenolic compounds are natural antioxidants found in plants that have various health benefits, including antioxidant activity. The study also explored the cytotoxic activity of *Crinum latifolium L.*, where it was possible to verify the substance's ability to cause damage to cells, which can have implications both in scientific research and medical applications (Aziz et al., 2014).

The potential for the application of phytopharmaceuticals in topical pharmaceutical forms has also been evaluated. In a study conducted to evaluate the healing activity of an ointment containing *Crinum zeylanicum* bulb extract, it was possible to obtain a satisfactory result at the end of the study because it did not present acute dermal toxicity, in addition to promoting wound retraction and epithelialization in rats, allowing the healing mechanism to be faster and better (Tijani et al., 2012).

The effects of cytotoxicity have been cited in several studies, mainly due to the promising potential for combating cancer cells. In the study conducted by Masi et al. (2019), it was possible to prove that flavonoids and coumarin derivatives are capable of exerting toxic activity for cancer cells, in addition to protecting HaCat cells against oxidative stress. The tests were conducted using HeLa and A431 cancer cell lines. N-p-coumaroyltyramine was toxic to cancer cells. Furthermore, the flavonoid derivatives showed AChE inhibition activity and the coumarin derivative showed inhibition of α-amylase and β-–glucosidase, tests were conducted at concentrations up to 50 µM.

As mentioned in previous works, the neuroprotective function of plants in this family has been constantly noted, it was the objective of a study that evaluated the potential for neuroprotection in vitro in addition to antioxidant activities and cytotoxicity of *Crossyne flava* extract and isolated alkaloids, the result obtained showed that the extract and all compounds presented neuroprotection by attenuating ATP levels in cells and inhibiting apoptosis induced by MPP+. To determine the optimal dose of *C. flava* and compounds that will show neuroprotection, a cell viability assay was performed in the SH-SY5Y cells treated with 2.5, 5, and 10 µg/mL of either *C. flava* extract or compounds. The results show that the total extract induced a dose-dependent reduction in cell viability, which was only significant at the 5 and 10 µg/mL concentrations (Omoruyi et al., 2021a).

In the study by Tayoub et al. (2018) it was possible to evaluate the antiproliferative effects of Pancratium maritimum extracts on MDA-MB-321 cells *Pancratium maritimum* L Extracts from bulbs and leaves of *Pancratium maritimum*, in which the ability to inhibit the proliferation of MDA-MB- cells was identified. 321, through cell arrest in the S and G2/M phases. The extracts also affected the expression of Cyclin B1, Bcl-2 and Ki67. The IC_{50} values were 0.039, 0.035, and 0.026 mg/ml after 48, 72, and 96 hours of treatment with 0.1 mg/ml concentration of bulb extract, respectively.

Those values were 0.051 and 0.03 mg/ml after 72 and 96 hours for root extract, respectively, and 0.048 mg/ml after 96 hours for flower extract.

A study that evaluated the cytotoxicity and antioxidant activity of whole plant extracts of Pancratium triflorum demonstrated that silver nanoparticles containing acetone extract from A. sativum bulbs showed larvicidal activity against 2nd and 3rd instar larvae of Aedes aegypti. What also enhances the promising area of combating arboviruses, in this study the larvicidal activity of A. sativum extract or green AgNPs synthesized from the extract was evaluated, each diluted in five different concentrations, 50, 100, 150, 200 and 250 ppm in distilled water (Nasir et al., 2022)

3.2. Toxicology

Due to the presence of isoquinoline alkaloids with toxic activity in humans, Amaryllidaceae species, such as *Boophone disticha*, *Clivia miniata*, *Crinum bulbispermum, Cotyledon orbiculta* var. *orbiculata* and *Scadoxus puniceus* cause symptoms such as dizziness, hypotension, convulsion, vomiting, diarrhea, salivation, nausea, respiratory arrest, visual disturbances, central nervous system (CNS) depression, gastrointestinal disturbance, restlessness, dyspnea, loss of coordination, dry mouth, blood and water accumulation in the lungs, bleeding of the intestinal mucosa, hallucinations, and coma, all of which can lead to death (Ndhlala et al., 2013).

Although their toxic effects should not be neglected, many alkaloids have potential pharmacological properties for treating various diseases. Most groups of alkaloids are known to affect signal transduction in brain neurons, either by modulating neurotransmitters, hormone receptors or their reuptake in presynaptic neurons, which characterizes them as potential drugs for treating systemic diseases (Rojas-Vera et al., 2021).

Boophone disticha, an endemic plant of the savannas, is considered extremely poisonous, although it was listed among the most medicinally traded plants in the great fairs and free trade centers worldwide. In most severe cases of intoxication, this species can cause dizziness, restlessness, impaired vision, unsteady walking, visual hallucinations, coma, and even death (Adewusi et al., 2012). By investigating the cytotoxicity and acetylcholinesterase inhibitory activity of an alkaloid crinine-type isolated from *Boophane disticha*, the degree of toxicity of the plant and risk to health if misused and with proper characterization processes were observed (Adewusi et al., 2012). The study used a methanolic extract from bulbs, and to assess cytotoxicity, the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium) assay was used. This assay is commonly employed to measure cell viability and proliferation capacity. It involves the conversion of the MTT salt into insoluble formazan by active mitochondrial enzymes in metabolically active cells (Adewusi et al., 2012).

Another clear example of the risk of poisoning is that of *Scadoxus puniceus,* commonly used as an aphrodisiac plant. This plant is also indicated by popular knowledge in some regions of the world, mainly Africa, as an effective plant to guarantee a safe pregnancy. However, it can provoke dizziness, visual disturbances, and CNS depression. The study was conducted using ethanol extracts, with leaves and bulbs of the plants, however the dose used was not clear (Ndhlala et al., 2013).

4. Conclusion

Despite the negative characteristics of the plants identified, the significance and importance of the Amaryllidaceae plant family in the discovery of phytochemical-based drugs has been demonstrated and is a highlight for pharmacologists worldwide. The commercialization of the first drug used to treat Alzheimer's disease has been highlighted, reinforcing its pharmacological potential. In addition, several other interesting biological properties, such as antimicrobial and anti-inflammatory activities, make the Amaryllidaceae family an interesting target for drug discovery. Nevertheless, surveillance is necessary to monitor the toxicological effects of bioactive compounds in this family, the alkaloids. Thus, its medicinal potential is promising for the pharmaceutical industry.

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