

Antitumor evaluation of amaryllidaceae alkaloids on cancer cell lines: A literature review

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Citation: Martins de Paiva MJ, do Nascimento GNL, de Melo Damasceno IA, Cunha LNB, de Sousa Pimentel JE, e Silva LTF, Castro TD, Silveira D. Antitumor evaluation of amaryllidaceae alkaloids on cancer cell lines: A literature review. *Electron J Gen Med.* 2024;21(1):em562. <https://doi.org/10.29333/ejgm/14040>

ARTICLE INFO

Received: 20 Aug. 2023

Accepted: 03 Oct. 2023

ABSTRACT

Amaryllidaceae alkaloids have attracted significant attention in cancer research for their potential antitumor properties. To date, numerous studies have investigated the effects of these alkaloids on cancer cell lines, but a comprehensive synthesis of the existing evidence through a literature review is warranted. This article presents a comprehensive literature review aimed at evaluating the antitumor effects of amaryllidaceae alkaloids on various cancer cell lines and elucidating the underlying mechanisms of action. A search was conducted in major scientific databases, including Google Scholar, PubMed, Scopus, and Web of Science, to identify relevant studies published between 2013 and 2023. Studies that examined the antitumor effects of amaryllidaceae alkaloids on cancer cell lines were included in the review. Data were extracted, analyzed, and synthesized to provide an in-depth overview of the findings. The alkaloids exhibited potent cytotoxicity and suppressed cell proliferation in a concentration-dependent manner. Mechanistic investigations unveiled that amaryllidaceae alkaloids induced apoptosis, cell cycle arrest, and hindered angiogenesis in cancer cells. Moreover, they demonstrated favorable selectivity towards cancer cells, sparing normal cells, suggesting potential as targeted therapies. This literature review consolidates and critically appraises the available evidence on the antitumor effects of amaryllidaceae alkaloids on cancer cell lines. The findings underscore their potential as promising candidates for further exploration in cancer therapeutics. Future preclinical and clinical studies are vital to advance their development and translation into effective anticancer drugs.

Keywords: Amaryllidaceae, alkaloids, antitumor effects, cancer cell lines, apoptosis, angiogenesis

INTRODUCTION

Plants from the Amaryllidaceae family have been extensively studied due to the presence of various pharmacologically active alkaloids. Among these compounds, amaryllidaceae alkaloids have gained attention for their potential antitumor activities. This botanical family harbors several species rich in alkaloids, such as crinine, lycorine, narciprimine, and galantamine, which have been subject to increasing interest in oncological research [1].

The pursuit of novel cancer treatments has propelled the investigation of natural compounds from plant sources, and amaryllidaceae plants emerge as promising reservoirs of bioactive compounds [2]. Previous studies have reported that these alkaloids may exert selective cytotoxic effects on different cancer cell lines, inhibiting proliferation and inducing apoptosis in tumor cells [3]. This profile of activity positions them as potential candidates for the development of new anticancer therapies [4].

The utilization of natural compounds from plants has garnered attention as it offers an innovative and less toxic approach to combating cancer, minimizing the side effects associated with conventional treatments [5]. However, despite their therapeutic potential, challenges remain, such as determining the effective dose, assessing toxicity, and understanding the bioavailability of these compounds [6, 7].

In this context, the present review aims to consolidate the available scientific evidence on the antitumor effects of amaryllidaceae alkaloids on cancer cell lines. Through critical analysis of the literature, we hope to provide a comprehensive overview of the pharmacological properties of these compounds, their therapeutic potential, and the challenges to be overcome for their clinical application. Understanding the mechanisms of action of these alkaloids and investigating potential combinations with existing therapies may contribute to advancing the search for new strategies in cancer treatment.

MATERIALS & METHODS

Search Strategy

For this literature review, a comprehensive search was conducted to identify relevant studies on the antitumor effects of amaryllidaceae alkaloids on cancer cell lines. The search strategy involved electronic databases, including Google Scholar, PubMed, Scopus, and Web of Science. The search terms used were a combination of medical subject headings and keywords related to amaryllidaceae alkaloids and cancer. The search was limited to articles published between January 2019 and January 2023. The following search terms and their variations were used: “amaryllidaceae alkaloids,” “anticancer activity,” “antitumor effects,” “cancer cell lines,” “in vitro studies,” “alkaloids,” “neoplastic cells,” and “tumor inhibition.”

Study Selection

Articles were screened for eligibility based on their titles and abstracts. Studies were included if they met the following criteria:

- (1) investigated the antitumor effects of amaryllidaceae alkaloids on cancer cell lines,
- (2) performed *in vitro* experiments,
- (3) published in English, and
- (4) available as full-text articles.

Studies involving animal models or clinical trials were excluded from the review. Two independent reviewers conducted the initial screening, and any discrepancies were resolved through discussion and consensus.

Data Extraction

Data from the selected studies were extracted using a standardized data extraction form. The following information was collected from each study: authors' names, publication year, study design, type of amaryllidaceae alkaloids tested, cancer cell lines used, methods of alkaloid administration, concentrations tested, treatment duration, and key findings related to the antitumor effects.

Data Analysis

A qualitative synthesis of the findings was performed. The antitumor effects of amaryllidaceae alkaloids on different cancer cell lines were summarized, highlighting the observed outcomes and potential mechanisms of action. The data were categorized based on the types of alkaloids tested and the types of cancer cell lines used in the experiments.

Quality Assessment

The methodological quality of the included studies was assessed using the Joanna Briggs Institute critical appraisal tools for experimental studies. This assessment aimed to evaluate the risk of bias and the quality of evidence presented in the selected studies. The quality assessment was independently performed by two reviewers, and any disagreements were resolved through discussion and consensus.

Data Synthesis

The extracted data were synthesized to provide a comprehensive overview of the current evidence on the

antitumor effects of amaryllidaceae alkaloids on cancer cell lines. The findings were presented in tabular form, and the results from individual studies were discussed in the context of the overall findings of the review.

Limitations

It is important to acknowledge potential limitations of this literature review. The search was limited to articles published in English and may have excluded relevant studies in other languages. Additionally, the review focused on *in vitro* studies and did not consider *in vivo* or clinical trials, which could limit the generalizability of the findings. The quality and heterogeneity of the included studies were also considered when interpreting the results.

RESULTS

Antitumor Effects of Amaryllidaceae Alkaloids

The literature review identified a total of 25 studies that investigated the antitumor effects of amaryllidaceae alkaloids on various cancer cell lines. The majority of the studies focused on alkaloids extracted from different Amartllidaceae plant species, including *Galanthus*, *Lycoris*, and *Nacissus*. These alkaloids demonstrated a wide range of pharmacological activities with potential therapeutic effects against cancer.

DISCUSSION

Inhibition of Cancer Cell Proliferation

Several studies reported significant inhibition of cancer cell proliferation by amaryllidaceae alkaloids. For instance, alkaloids from *Galanthus* species showed dose-dependent growth inhibitory effects on breast cancer cells (MCF-7), prostate cancer cells (PC-3), and colon cancer cells (HCT116). Additionally, lycorine, an alkaloid isolated from *Lycoris* species, exhibited potent antiproliferative activity against lung cancer cells (A549) and leukemia cells (K562). These findings suggest that amaryllidaceae alkaloids possess promising anticancer properties and can be potential candidates for novel therapeutic interventions [2-4, 8, 18, 22, 25].

Induction of Apoptosis

The mechanism underlying the antitumor effects of amaryllidaceae alkaloids was extensively studied, and apoptosis was identified as a key pathway involved. Several alkaloids, such as haemanthamine and homolycorine, induced apoptotic cell death in different cancer cell lines. Activation of caspases and downregulation of anti-apoptotic proteins, such as Bcl-2, were observed, indicating the involvement of intrinsic apoptotic pathways. Moreover, amaryllidaceae alkaloids were found to trigger the release of cytochrome c from mitochondria, leading to caspase activation and apoptosis. These findings support the potential of amaryllidaceae alkaloids as effective agents for inducing cancer cell death [4, 9, 10-13].

Anti-Inflammatory Properties

The discovery of the anti-inflammatory properties of amaryllidaceae alkaloids adds an intriguing dimension to their potential as anticancer agents [14-16]. Inflammation is an

Table 1. Distribution of articles selected for review

Reference	Alkaloid type	Cancer type	Plant used	Conclusions
[18]	Lycorine	Gastric cancer	<i>Lycoris radiata</i> (L'Hér.) Herb	The cytotoxic effect on MKN-45 and SGC-7901 cells is due to down-regulation of MCL1, up-regulation ubiquitin E3 ligase FBXW7. Moreover Lycorine, in synergism with HA14-1 (inhibitor of BCL2), exhibited anti-tumor activity, in vivo.
[24]	Lycorine	Tumor blood vessels	-	The cytotoxic effect on HUVECs cells is due to inhibition of cellular migration and tube formation.
[30]	Lycorine hydrochloride	Ovarian cancer	-	The cytotoxic effect is due to the inhibition of mitotic proliferation of Hey1B cells, down-regulation of cyclin D3 expression, and suppression of the formation of capillary-like tubes.
[8]	Narciclasine	Esophageal cancer	<i>Lycoris sanguinea</i> Maxim.	Narciclasine affects FAK distribution and phosphorylation, inhibiting cell proliferation and migration. FAK/JNK and p38 pathway are also involved in the cell inhibition mechanism.
[19]	Narciclasine	Narciclasine	-	Cytotoxicity occurs through down-regulation of L-17A/Act1/TRAF6/NF- κ B anti-apoptotic signaling pathway.
[7]	Haemantamine and Haemantidine	Leukemia	<i>Habranthus robustus</i> Herb.	Haemantamine and haemantidine inhibit cell proliferation, increasing apoptosis and caspases activation, decreasing mitochondrial membrane potential and arresing the cell cycle in p53-null T cell leukemia Jurkat cells.

essential characteristic of the tumor microenvironment, playing a pivotal role in the development, progression, and dissemination of cancer [17]. Amaryllidaceae alkaloids, such as lycorine and crinine, have demonstrated the ability to modulate inflammatory responses, which could have a significant impact in the context of cancer [16, 18].

The modulation of pro-inflammatory cytokines such as TNF- α (tumor necrosis factor alpha), IL-6 (interleukin-6), and IL-1 β (interleukin-1 beta), by amaryllidaceae alkaloids suggests that these compounds may have a regulatory effect on the inflammatory response within the tumor environment [19]. These cytokines are often overexpressed in cancer cells and the tumor microenvironment, contributing to angiogenesis promotion, invasion of surrounding tissues, and metastasis [20]. By inhibiting the production or activity of these pro-inflammatory cytokines, amaryllidaceae alkaloids could potentially reduce tumor-associated inflammation and, consequently, diminish disease progression [21].

The anti-inflammatory effect of amaryllidaceae alkaloids could impact not only cancer cells directly but also influence immune cells present in the tumor microenvironment [22]. Modulation of immune responses can profoundly affect the interaction between cancer cells and immune cells, potentially influencing the immune system's ability to recognize and eliminate tumor cells [23, 24]. This intricate interplay between inflammation, the immune system, and cancer suggests that the anti-inflammatory effects of amaryllidaceae alkaloids might have profound implications for cancer treatment and prevention [25].

Synergistic Effects With Chemotherapy

Several studies explored the potential synergistic effects of amaryllidaceae alkaloids with conventional chemotherapeutic agents [26]. Co-administration of alkaloids with cisplatin, doxorubicin, and paclitaxel resulted in enhanced cytotoxic effects on cancer cells [27]. Furthermore, combination therapy with amaryllidaceae alkaloids was found to sensitize drug-resistant cancer cells, overcoming chemoresistance [28]. These findings suggest that amaryllidaceae alkaloids could be utilized as adjuvants to improve the efficacy of standard cancer treatments [29].

Mechanisms of Drug Resistance

While amaryllidaceae alkaloids demonstrated significant antitumor effects, some studies also explored the potential mechanisms of drug resistance [30]. Upregulation of drug efflux pumps such as P-glycoprotein, was observed in cancer cells treated with alkaloids, leading to reduced intracellular drug accumulation and resistance to apoptosis [31]. Understanding these resistance mechanisms is crucial for developing strategies to overcome drug resistance and improve the effectiveness of amaryllidaceae alkaloids as anticancer agents [32]. The present literature review provides valuable insights into the antitumor effects of amaryllidaceae alkaloids on cancer cell lines [33]. The studies reviewed demonstrated that these alkaloids possess significant growth-inhibitory effects and induce apoptosis in various cancer cell types. The activation of apoptotic pathways and the downregulation of anti-apoptotic proteins indicate their potential as effective agents for inducing cancer cell death [4, 11, 18, 20, 34].

Furthermore, the anti-inflammatory properties of amaryllidaceae alkaloids suggest their potential role in attenuating tumor-associated inflammation. By modulating inflammatory responses, these alkaloids may contribute to the suppression of tumor growth and metastasis [21]. Additionally, their ability to sensitize drug-resistant cancer cells opens up new avenues for overcoming chemoresistance and improving the outcomes of conventional chemotherapy [22-24]. The results also highlight the potential synergistic effects of amaryllidaceae alkaloids with standard chemotherapeutic agents. Combination therapy with alkaloids has shown promise in enhancing the cytotoxic effects of conventional drugs, making them potential adjuvants for cancer treatment [25, 26, 35]. However, despite the promising findings, some studies revealed the emergence of drug resistance mechanisms in response to amaryllidaceae alkaloid treatment. Understanding these resistance pathways is crucial for devising strategies [27, 36].

CONCLUSIONS

Despite promising results in antitumor studies with amaryllidaceae alkaloids, gaps still require attention. Pre-clinical and clinical trials, pharmacokinetics, stable formulations, and drug interactions are essential to validate their clinical use. Identifying active compounds, understanding mechanisms of action and molecular targets is also crucial. Overcoming these challenges can lead to innovative oncology therapies and improvements in patients' quality of life.

Author contributions: **MJMP:** responsible for research design, literature review, data collection, & analysis related to antitumor activity of amaryllidaceae alkaloids on cancer cell lines; **GNLN:** conducted selection of scientific articles for literature review, participated in result discussions, & contributed to writing of article; **IAMD:** performed critical analyses of studies included in review, assisted in discussion of mechanisms of action of alkaloids, & contributed to formulation of conclusions; **LNBC:** conducted statistical analyses of collected data & contributed to interpretation of results; **JESP & TDC:** participated in identification & selection of amaryllidaceae alkaloids discussed in review, as well as in discussion of their potential antitumor properties; **LTFS:** performed critical analyses of studies included in review, assisted in discussion of mechanisms of action of alkaloids, & contributed to formulation of conclusions; & **DS:** worked on manuscript review & editing, ensuring text consistency & coherence, & assisted in article submission for publication. All authors have agreed with the results and conclusions.

Funding: The authors would like to thank Fundação de Amparo à Pesquisa do Distrito Federal (FAP-DF, process 00193-00002304/2022-79), Universidade de Gurupi, and Universidade de Brasília (UnB) for the financial support.

Ethical statement: The authors stated that the study did not require ethical approval. It is a review article on existing literature.

Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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