Journal of Molecular and Pharmaceutical Sciences

Review

Next-generation anticancer agents from the amaryllidaceae family: design, optimization, and nano-delivery strategies for clinical translation

Bechlem Houria [a*], Bougandoura Amina Daryne [a], Bahi Meriem [a], Benouchenne Djamila [b,c]

[a] *Pharmaceutical Sciences Research Center (CRSP), Constantine 25000, Algeria.*

[b] *Laboratoire de Génétique Biochimie et Biotechnologies Végétales, Faculté des Sciences de la Nature et de la Vie, Université Frères Mentouri Constantine 1, Constantine 25000, Algeria*

[c] *Higher National School of Biotechnology Taoufik Khaznadar, Nouveau Pôle Universitaire Ali Mendjeli, BP. E66, Constantine 25100, Algeria*

Abstract

Amaryllidaceae alkaloids represent a distinctive class of plant derived anticancer agents, characterized by exceptional molecular potency and unconventional mechanisms of action. Despite decades of intensive investigation including extensive structure–activity relationship (SAR) studies, none have successfully translated into clinically approved anticancer therapies. This persistent gap reflects not a lack of efficacy, but recurrent chemotype specific barriers arising from rigid polycyclic architectures, narrow structure activity relationship windows, unfavourable pharmacokinetics, and mechanism linked toxicity. Here, we critically examine the translational trajectory of major Amaryllidaceae alkaloid chemotypes, integrating structural, SAR, pharmacokinetic, and formulation evidence to explain why classical potency driven optimization has repeatedly failed. Across lycorine, haemanthamine, narciclasine, and crinine-type scaffolds, medicinal chemistry efforts are constrained by stereochemical inflexibility and exposure limitations that cannot be resolved through scaffold modification alone. In this context, nano-enabled delivery emerges as a conditional, exposure-oriented strategy capable of improving biodistribution and tolerability, but only when aligned with permissive SAR and manageable toxicity profiles. Rather than cataloguing compounds or technologies, this review advances a translation-oriented framework that emphasizes early PK and toxicity aware lead prioritization, rational selection between chemical optimization and formulation strategies, and timely scaffold triage. By reframing Amaryllidaceae alkaloid development through feasibility driven decision making, this perspective offers a pragmatic blueprint for reducing attrition and accelerating the clinical advancement of structurally complex natural products.

Keywords

Amaryllidaceae, alkaloids, anticancer, natural products

*Received November 25, 2025; accepted December 25, 2025

Corresponding author

Email: bechlem.houria@crsp.dz (Bechlem Houria)

Cited as: Bechlem H, Bougandoura A.D, Bahi M, Benouchenne D. Next-generation anticancer agents from the amaryllidaceae family: design, optimization, and nano-delivery strategies for clinical translationJ. Mol. Pharm. Sci. 04 (02), 2025, 84-97.

1 Introduction

Plant derived natural products have historically played a central role in anticancer drug discovery, providing structurally diverse scaffolds and mechanistically unique modes of action that remain difficult to replicate through purely synthetic approaches. Despite a recent shift toward targeted therapies and biologics, small-molecule anticancer agents particularly those originating from complex natural frameworks, continue to represent a major source of clinically effective drugs [1]. Within this landscape, alkaloids stand out as a privileged class, combining high biological potency with intricate three-dimensional architectures capable of engaging essential cellular machineries [2].

Among alkaloid producing plant families, the Amaryllidaceae occupy a singular position. Their characteristic isoquinoline derived alkaloids, collectively referred to as Amaryllidaceae alkaloids (AAs) [3], display remarkable structural diversity and broad-spectrum anticancer activity across multiple cellular models [4]. Compounds such as lycorine, haemanthamine, narciclasine, crinine, and galanthamine-derived analogues have been shown to interfere with fundamental processes including ribosomal function, protein synthesis, cytoskeletal dynamics, and cell cycle progression [5]. These mechanisms often distinct from those of clinically approved cytotoxic have positioned AAs as attractive candidates for next-generation anticancer strategies [6].

Paradoxically, however, this strong preclinical promise has not translated into clinical success. Despite decades of investigation and numerous reports describing nanomolar cytotoxicity and compelling mechanistic insights, Amaryllidaceae alkaloids remain conspicuously absent from the anticancer pharmacopeia [3]. This discrepancy highlights a persistent and underexplored paradox in anticancer drug discovery: exceptional *in vitro* potency does not necessarily predict clinical relevance [14,83]. For AAs, intrinsic scaffold liabilities including high polarity, rigid polycyclic architectures, narrow therapeutic indices, and unfavourable pharmacokinetic profiles have repeatedly undermined translational progression [7].

Historically, research on Amaryllidaceae alkaloids has been dominated by potency-driven paradigms, prioritizing cytotoxic activity over drug-like properties and early translational feasibility [3]. As a result, many promising AA leads advanced deep into preclinical pipelines only to encounter insurmountable barriers related to systemic exposure, off-target toxicity, metabolic instability, or insufficient tumour accumulation [8]. These challenges are further compounded by the mismatch between rodent-based pharmacokinetic models and human clinical realities, a limitation that has frequently led to overestimation of therapeutic potential [9].

In response to these obstacles, two complementary strategies have emerged over the past decade. The first focuses on rational chemical optimization, leveraging structure activity relationship (SAR) studies, [10] to modulate polarity, stereochemistry, and functional group orientation while preserving pharmacophoric integrity [11]. The second involves nanotechnology enabled delivery systems, designed to enhance tumour exposure, improve biodistribution, and mitigate systemic toxicity without fundamentally altering the bioactive scaffold [12]. While both approaches have generated encouraging preclinical outcomes, their true translational value and limitations remain insufficiently integrated into a coherent design framework.

Importantly, nano-delivery has often been presented as a universal solution to pharmacological shortcomings. Yet accumulating evidence suggests that nanocarriers cannot compensate for intrinsic scaffold toxicity or an inherently unfavourable therapeutic window [7]. Instead, nano-delivery should be viewed as a translational enabler, effective only when applied to chemically and pharmacologically viable leads [13]. This distinction is particularly critical for Amaryllidaceae alkaloids, where overreliance on delivery strategies risks masking, rather than resolving, fundamental liabilities.

In this review, we provide a critical and integrative analysis of Amaryllidaceae alkaloids as anticancer agents, moving beyond descriptive cataloguing toward a translation-oriented perspective. We first outline the structural and mechanistic diversity of major AA chemotypes and examine how specific architectural features govern biological activity [14]. We then analyse historical and emerging SAR driven optimization strategies, highlighting both successful modifications and recurrent dead ends [15]. Finally, we assess nano

delivery approaches through a realistic translational lens, delineating what these technologies can and cannot solve in the context of AA based drug development [1].

By explicitly addressing the disconnect between potency and clinical relevance, this review aims to redefine design priorities for Amaryllidaceae derived anticancer agents. We argue that future success will depend not on the discovery of increasingly potent analogues, but on the adoption of translation driven frameworks that integrate chemical optimization, pharmacokinetics, toxicity awareness, and rational delivery strategies from the earliest stages of development [7].

2 Structural and mechanistic diversity of Amaryllidaceae alkaloids

2.1 Biosynthetic origin and chemotaxonomic classification

Amaryllidaceae alkaloids originate from a conserved biosynthetic framework involving the aromatic amino acids *L*-phenylalanine and *L*-tyrosine, which are produced through the shikimate pathway in higher plants [16]. Subsequent enzymatic transformations, including decarboxylation, reduction, and oxidative phenolic coupling, give rise to the characteristic isoquinoline-derived scaffolds that define this family of natural products [17].

Recent advances have clarified the central role of cytochrome P450 enzymes, particularly CYP96T1-like monooxygenases, in governing regioselective para-para and para-ortho phenolic coupling reactions that dictate downstream scaffold formation [18]. These early biosynthetic branching points largely determine the emergence of distinct alkaloid chemotypes and underpin the strong chemotaxonomic value of Amaryllidaceae alkaloids, which has been extensively exploited in phytochemical and evolutionary studies [19].

2.2 Major alkaloid chemotypes

Lycorine-type alkaloids

Lycorine-type alkaloids are characterized by a rigid phenanthridine core bearing vicinal diol functionalities and a highly constrained polycyclic architecture [20]. This scaffold exhibits limited conformational flexibility and high polarity, features that contribute to strong target engagement but also impose significant pharmacokinetic liabilities. Lycorine and related analogues are among the most widely distributed AAs and serve as archetypal representatives of this chemotype [21].

Crinine-type alkaloids

Crinine-type alkaloids possess a β-crinane skeleton featuring a bridged tetracyclic framework with multiple stereo-genic centres [22]. Subtle variations in ring junction geometry and substituent orientation generate a diverse family of analogues with distinct physicochemical profiles [23]. This chemotype is widely represented across multiple Amaryllidaceae genera and has been the subject of extensive synthetic and semi-synthetic efforts [24].

Haemanthamine-type alkaloids

Haemanthamine-type alkaloids are structurally related to crinine derivatives but display distinct oxygenation patterns and ring fusion geometries that confer unique three-dimensional shapes [25]. These structural nuances are critical for high-affinity interactions with macromolecular targets and distinguish haemanthamine from other β-crinane frameworks [11].

Isocarbostyril (narciclasine-type) alkaloids

Isocarbostyril alkaloids, exemplified by narciclasine, feature a planar isocarbostyril core with minimal conformational freedom [26]. This chemotype is notable for its exceptional cytotoxic potency but also for its narrow therapeutic window, a direct consequence of its rigid architecture and limited opportunities for structural modulation [10].

Galantamine-type alkaloids

Galantamine-type alkaloids are structurally distinct from the highly cytotoxic Amaryllidaceae chemotypes and are characterized by a more flexible tetracyclic framework with improved physicochemical balance [27]. Their relatively favourable absorption, distribution, metabolism, and excretion (ADME) properties have enabled successful clinical translation in non-oncological indications, underscoring the importance of scaffold-level drug-likeness [28].

The structural diversity of Amaryllidaceae alkaloids is illustrated by representative members of the major chemotypes shown in Figure 1.

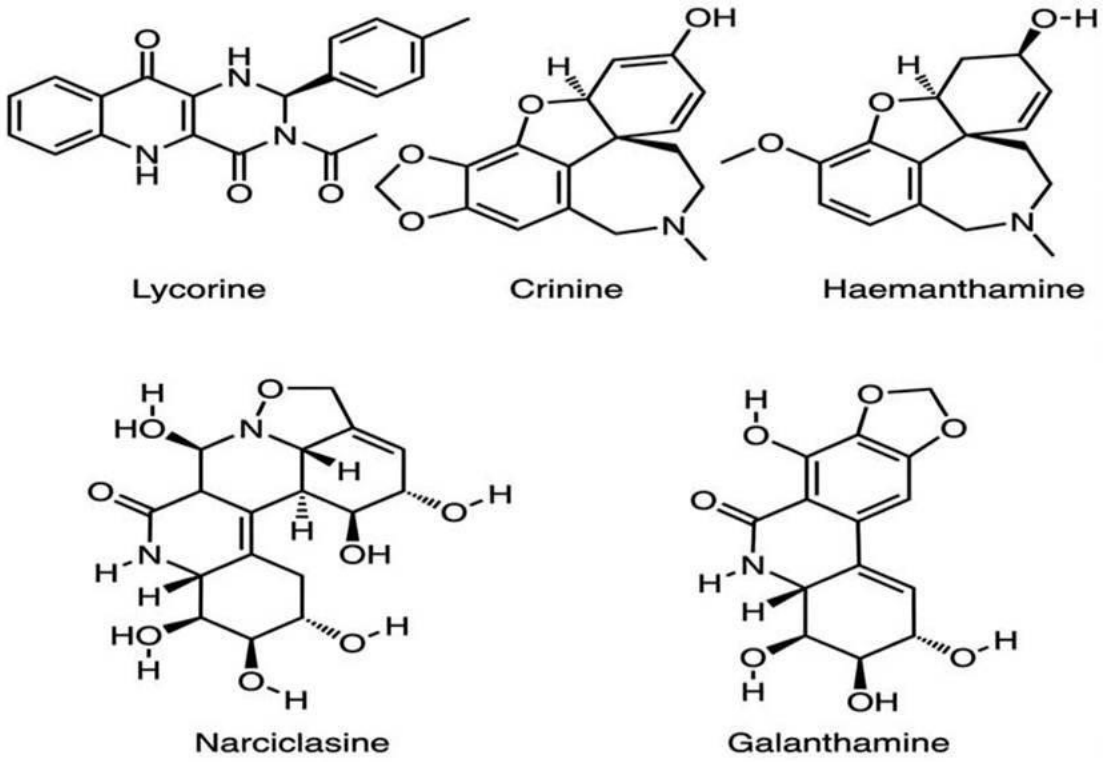

Figure 1. Representative Amaryllidaceae alkaloid structures.

2.3 Molecular targets and anticancer mechanisms

Ribosomal inhibition and suppression of protein synthesis

Several Amaryllidaceae alkaloids, most notably haemanthamine and narciclasine, exert their anticancer activity through direct binding to the eukaryotic ribosome, leading to inhibition of peptide bond formation and global suppression of protein synthesis [29]. Structural studies have revealed that these compounds target conserved ribosomal sites distinct from those exploited by clinically used translation inhibitors, providing a mechanistic basis for activity against drug-resistant cancer phenotypes [11].

Cytoskeletal disruption and inhibition of invasive behaviour

Lycorine-type alkaloids have been shown to interfere with actin dynamics and cytoskeletal organization, resulting in impaired cell motility, reduced invasion, and suppression of metastatic potential [20]. These effects are often accompanied by modulation of signalling pathways, [30] associated with cell adhesion and migration, including focal adhesion kinase (FAK) and extracellular signal-regulated kinase (ERK) cascades [31].

Cell-cycle arrest and stress-response signalling

Beyond direct macromolecular targeting, Amaryllidaceae alkaloids modulate multiple stress-response pathways, including signal transducer and activator of transcription 3 (STAT3) signalling, integrated stress responses, and apoptosis-related cascades [32]. While such pleiotropic activity may enhance anticancer efficacy, [6] it also complicates therapeutic index optimization and target validation, contributing to translational uncertainty.

The diverse molecular targets and anticancer mechanisms engaged by Amaryllidaceae alkaloids in cancer cells are summarized in Figure 2.

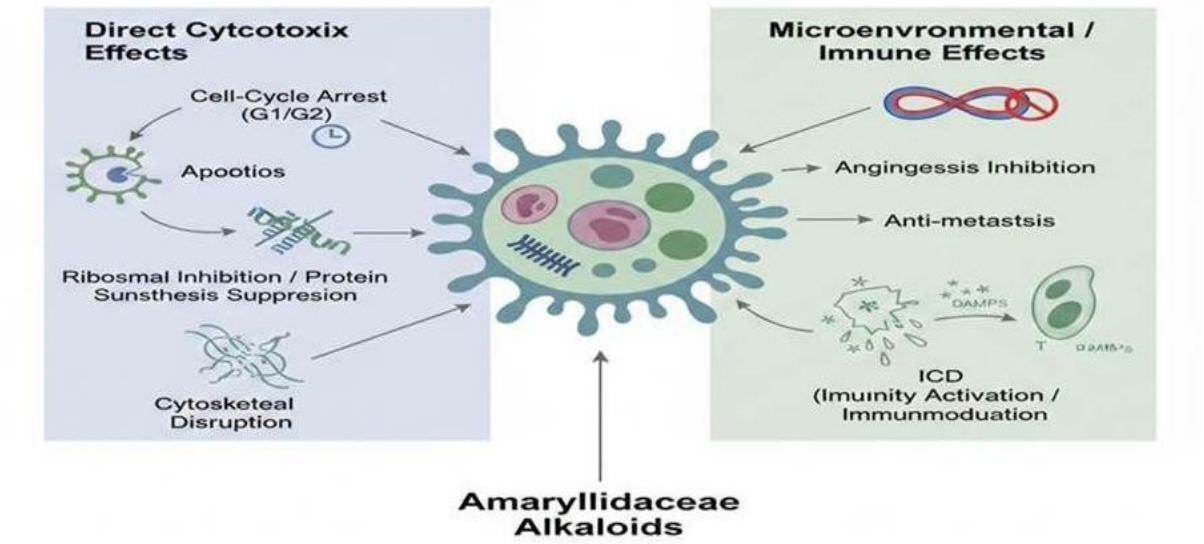

Figure 2. Mechanistic landscape of Amaryllidaceae alkaloids in cancer cells

Despite well-defined chemotypes and mechanistic sophistication, the clinical translation of Amaryllidaceae alkaloids has remained strikingly limited.

3. Challenges and limitations in the clinical translation of Amaryllidaceae alkaloids

3.1 Potency-driven discovery paradigms and misleading in vitro efficacy

Early research on Amaryllidaceae alkaloids was largely guided by potency-driven discovery paradigms [33], in which nanomolar cytotoxicity in two-dimensional cancer cell models served as the principal criterion for lead selection [34]. Numerous alkaloids, including lycorine, haemanthamine, and narciclasine type compounds, exhibited striking in vitro antiproliferative activity across diverse tumour cell lines[20], frequently surpassing reference chemotherapeutics [24].

However, such assays rarely accounted for pharmacologically relevant exposure, intracellular target engagement, or achievable systemic concentrations. Moreover, short-term viability assays often failed to distinguish cytostatic from cytotoxic effects, leading to inflated expectations of therapeutic efficacy[34]. This historical reliance on potency alone mirrors broader challenges in anticancer drug discovery, where early efficacy signals frequently fail to translate into durable clinical benefit [35].

3.2 Intrinsic scaffold liabilities driving poor drug-likeness of Amaryllidaceae alkaloids

From a chemical perspective, most Amaryllidaceae alkaloids possess highly polar, rigid polycyclic frameworks enriched in hydrogen bond donors and acceptors [17]. While these features promote strong interactions with biological targets, they severely restrict passive membrane permeability and oral absorption, as predicted by polar surface area and lipophilicity thresholds [9].

In addition, the dense stereochemical complexity of many AA chemotypes limits the accessible structure activity relationship (SAR) space [36]. Attempts to modulate polarity, metabolic stability, or permeability through semi-synthesis or total synthesis have often resulted in diminished activity or increased toxicity, reflecting the narrow tolerance of these scaffolds to chemical modification [37]. As a consequence, optimization toward drug-like properties has proven substantially more challenging than for flatter, more modular small molecule frameworks.

3.3 Narrow therapeutic windows and systemic toxicity

A defining limitation of Amaryllidaceae alkaloids is their consistently narrow therapeutic index. Core mechanisms such as ribosomal inhibition, global suppression of protein synthesis, and interference with cytoskeletal dynamics are inherently associated with toxicity in normal proliferative tissues [38]. Consequently, modest increases in systemic exposure frequently led to disproportionate adverse effects, including gastrointestinal, haematological, and neurological toxicities [39].

This liability has repeatedly constrained dose escalation in vivo, preventing sustained tumour exposure even when robust antitumor activity is observed in vitro. Importantly, the exceptional potency of isocarbostyril alkaloids such as narciclasine is inseparable from their toxicity profile, underscoring the difficulty of uncoupling efficacy from safety at the scaffold level [26].

3.4 Pharmacokinetic failure and inadequate tumour exposure

Unfavourable pharmacokinetic behaviour represents a further major barrier to clinical translation [8]. Many Amaryllidaceae alkaloids exhibit rapid clearance, extensive first-pass metabolism, and limited bioavailability following systemic administration [40]. High plasma clearance and suboptimal tissue distribution restrict effective tumour exposure, particularly in solid malignancies.

Notably, rodent pharmacokinetic models have frequently overestimated tolerability and systemic exposure relative to human physiology, contributing to translational disconnects between preclinical promise and clinical feasibility [41]. In contrast, galantamine characterized by comparatively balanced absorption, distribution, metabolism, and excretion (ADME) properties successfully achieved clinical translation in neurological indications, highlighting the decisive role of pharmacokinetics in determining clinical viability [42].

3.5 Target pleiotropy contributing to translational uncertainty

Many Amaryllidaceae alkaloids act through pleiotropic mechanisms, simultaneously modulating ribosomal function, stress-response signalling, apoptosis, and cytoskeletal organization [43]. While such multi-target activity may enhance anticancer efficacy, it complicates target validation, biomarker development, and patient stratification [44].

The absence of well-defined pharmacodynamic markers and exposure response relationships has further hindered rational clinical development. Without clear links between target engagement, dose and efficacy, the design of dosing regimens and clinical endpoints remains largely empirical, increasing the risk of late-stage attrition.

The limited clinical success of Amaryllidaceae alkaloids reflects not a lack of biological potency, but a persistent misalignment between scaffold properties, pharmacokinetics, and translational design requirements. These constraints are summarized in Table 1, which outlines the key physicochemical, pharmacokinetic, and mechanistic liabilities that have hindered clinical development across major Amaryllidaceae alkaloid chemotypes.

Table 1. Chemotype-Specific SAR Constraints, Optimization Attempts, and Translational Outcomes of Amaryllidaceae Alkaloids

Chemotype	Key pharmacophoric elements	Major SAR determinants	Typical optimization attempts	Recurrent failure modes	Actionable design rule	Key refs
Lycorine-type	Vicinal C-1/C-2 diols; rigid phenanthridine core	C-1 stereochemistry dictates ribosomal binding; free diol essential for activity	Diol esterification/etherification; ring truncation; polarity masking	Activity loss upon diol masking; rapid clearance; GI toxicity	Preserve C-1/C-2 diol; improve exposure via formulation, not scaffold alteration	[33],[21], [20], [40], [44]
Haemanthamine-type	5,10b-ethanophenanthridine scaffold; tertiary amine	Precise 3D geometry required for ribosome engagement	Peripheral semi-synthetic substitutions	Narrow SAR; PK gains offset by toxicity	Limit modifications to peripheral positions; core scaffold non-negotiable	[25], [45] ,[11]
Crinine-type	β-Crinane skeleton; polycyclic rigidity	Stereochemistry governs cytostatic vs cytotoxic profile	Ring substitution; enantioselective synthesis	Insufficient anticancer potency despite tractability	Deprioritize for oncology; consider CNS-oriented indications	[22], [46], [23], [24]
Narciclasine-type	Isocarbostyril core; essential phenolic OH groups	Ribosomal inhibition tightly coupled to toxicity	C-1/C-6 derivatization; aza-analogues	Potency–toxicity inseparability; narrow therapeutic index	Avoid potency optimization; only delivery-based risk mitigation feasible	[47], [26], [48], [10], [13]
Galanthamine-type	Tetracyclic scaffold; optimized polarity	CNS penetration driven by optimal PSA/logP balance	O-demethylation control; metabolic optimization	Limited anticancer relevance despite favourable PK	Clinical success driven by PK, not anticancer potency	[14], [42], [28], [49]

4. Rational Chemical Optimization Strategies

4.1 SAR constraints imposed by rigid polycyclic scaffolds

Across Amaryllidaceae alkaloid chemotypes, medicinal chemistry efforts have been fundamentally constrained by the high rigidity and dense three dimensional architecture of their polycyclic cores[17]. Comprehensive chemotaxonomic and SAR analyses have consistently highlighted that AA frameworks tolerate only minimal perturbation without compromising biological activity [4].

Unlike flexible synthetic cytotoxic, AA scaffolds exhibit exceptionally narrow structure–activity relationship (SAR) windows, particularly for lycorine and haemanthamine-type alkaloids, where even subtle alterations in ring junction geometry or hydroxyl orientation result in abrupt loss of potency [33]. Structural biology and synthetic studies further confirm that the global three-dimensional architecture not isolated functional motifs dictates productive target engagement [50].

Historical optimization campaigns frequently attempted scaffold simplification, partial ring truncation, or core rearrangement to improve drug-likeness and synthetic accessibility. However, these approaches consistently failed to preserve anticancer activity, underscoring that AA bioactivity is inseparable from their intact polycyclic architecture.[51]As summarized in Table 1, productive optimization has therefore remained limited to peripheral modifications that preserve the global conformation required for biological function.

4.2 Stereochemical and functional group determinants of activity

Stereochemical integrity emerges as a dominant determinant of anticancer activity across AA chemotypes. For lycorine-type alkaloids, the absolute configuration at C-1 and its associated vicinal diol dictates ribosomal binding geometry and translational inhibition [38]. Masking, inverting, or chemically modifying this motif invariably abolishes activity, despite occasional gains in lipophilicity or metabolic stability [37].

Similarly, haemanthamine-type alkaloids display extreme sensitivity to stereochemical distortion, reflecting a binding mode that relies on precise spatial complementarity with the eukaryotic ribosome rather than high affinity interactions alone [45]. These observations explain why classical medicinal chemistry strategies such as bioisosteric replacement or aggressive functional group swapping have yielded limited success across AA subclasses [52].

Collectively, SAR analyses converge on a central principle: pharmacophoric elements in Amaryllidaceae alkaloids are not modular and cannot be optimized independently without disrupting the global binding geometry required for activity.

4.3 Polarity modulation and exposure-driven design

High polarity and suboptimal membrane permeability represent recurrent liabilities for several AA subclasses, particularly lycorine and narciclasine-type compounds [7]. Early optimization efforts focused on masking polar functionalities to enhance passive diffusion and oral absorption [9]. While such approaches occasionally improved in vitro permeability metrics, they almost invariably disrupted target engagement or exacerbated systemic toxicity [47].

These outcomes highlight a critical shift in design philosophy: for Amaryllidaceae alkaloids, systemic exposure not intrinsic potency is the primary driver of in vivo efficacy [42]. Galantamine exemplifies this principle, where clinical success derives from a balanced physicochemical and pharmacokinetic profile rather than exceptional potency [53].

Consequently, exposure driven design strategies such as careful polarity tuning, prodrug approaches, or formulation-based solutions have proven more effective than direct scaffold modification for improving translational potential [54].

4.4 Dead ends and non-productive modification pathways

A defining feature of AA medicinal chemistry is the recurrence of non-productive optimization pathways[26]. In narciclasine analogues, potency enhancement consistently correlates with increased cytotoxicity and a narrowing therapeutic window, indicating that efficacy and safety are mechanistically inseparable for this chemotype [48].

Similarly, extensive derivatization of crinine-type alkaloids has yielded chemically tractable analogues with improved physicochemical properties, yet limited anticancer relevance or insufficient therapeutic indices [55]. These outcomes reinforce that not all AA chemotypes warrant equal investment for oncology applications [56].

Collectively, these dead ends support a central conclusion summarized in Table 1: translation-oriented optimization requires early recognition of chemotypes for which classical medicinal chemistry cannot overcome intrinsic biological constraints. Rather than indiscriminately expanding chemical diversity, successful optimization of Amaryllidaceae alkaloids demands early triage based on SAR rigidity, stereochemical sensitivity, and exposure limitations.

Under these conditions, formulation-based strategies, including nano-enabled delivery systems, emerge as a plausible alternative pathway to address exposure and tolerability constraints without altering the core pharmacophore. Whether such approaches can meaningfully extend the therapeutic window of structurally rigid AA chemotypes remains an open question.

5. Nano-Enabled Delivery of Amaryllidaceae Alkaloids: Opportunities and Limitations

5.1 Exposure-driven rationale for nano-delivery

For most Amaryllidaceae alkaloids, translational failure has not arisen from insufficient intrinsic potency but from inadequate systemic exposure and unfavourable biodistribution profiles [7]. High polarity, rapid clearance, and narrow therapeutic windows have collectively limited effective dose escalation for lycorine- and narciclasine-type scaffolds, despite robust anticancer activity in vitro [47].

Nano-enabled delivery has therefore emerged not as a potency enhancing strategy, but as an exposure control intervention, aimed at prolonging circulation time, reducing off-target toxicity, and improving tumour accumulation through pharmacokinetic modulation rather than chemical optimization. This rationale aligns with broader trends in natural product based nanomedicine, where formulation engineering compensates for structural immutability [57].

5.2 Polymeric nanoparticles, lipid-based carriers, and conjugates

Polymeric nanoparticles, including PEGylated and biodegradable matrices, have been the most frequently explored carriers for AA delivery, offering protection from metabolic degradation and sustained release profiles [13]. Lipid-based systems particularly liposomes provide complementary advantages, such as improved biocompatibility and enhanced tumour uptake via passive targeting mechanisms [54].

Conjugation based approaches, including prodrug and peptide-linked systems, further enable stimulus responsive release triggered by tumour-specific cues such as pH, redox gradients, or enzymatic activity [58].While these platforms differ in complexity and translational maturity, they share a common objective: decoupling pharmacological activity from unfavourable physicochemical properties inherent to AA scaffolds.

5.3 Potential roles of nano-enabled delivery in addressing translational barriers

Nano-delivery systems can effectively address several recurring liabilities of Amaryllidaceae alkaloids. First, they improve apparent solubility and systemic stability without chemically masking critical pharmacophores[12]. Second, controlled release profiles reduce peak plasma concentrations, mitigating acute toxicity while preserving antitumor exposure [54].

Third, nano-carriers enable selective tumour accumulation through enhanced permeability and retention effects or ligand mediated targeting, partially compensating for the absence of intrinsic selectivity in many AA chemotypes[59]. Collectively, these benefits reposition nano-delivery as a translation enabling strategy, particularly for rigid scaffolds that resist productive medicinal chemistry optimization.

5.4 Translational barriers not addressed by nano-enabled delivery

Critically, nano-delivery does not resolve fundamental SAR constraints. Formulation strategies cannot rescue compounds whose activity depends on exposure levels incompatible with systemic safety, as observed for narciclasine and certain lycorine derivatives [47]. Nor can nano-carriers compensate for excessive on-target toxicity arising from ribosomal inhibition in normal tissues [29].

Moreover, nano-delivery does not alter intrinsic mechanism of action, stereochemical dependency, or therapeutic window width parameters that remain governed by molecular structure rather than formulation [46]. These limitations underscore a central principle: nano-delivery extends translational viability only when aligned with permissive SAR and manageable toxicity profiles.

Taken together, these considerations underscore that nano-enabled delivery represents a contextual enabler rather than a universal solution. Effective translation of Amaryllidaceae alkaloids therefore depends on integrating chemical tractability, delivery feasibility, and early PK–toxicity signals into a unified prioritization strategy. This perspective provides the basis for the decision-orientation.

6. Integrative design framework for clinical translation

6.1 Early PK- and toxicity-aware lead prioritization

The recurrent translational failure of AAs underscores the necessity of early pharmacokinetic and toxicity informed prioritization, rather than potency driven selection. Despite extensive in vitro cytotoxicity data across multiple AA chemotypes, systemic exposure and metabolic stability frequently remain insufficient for in vivo efficacy [40]. Metabolic studies on galantamine and lycorine demonstrate rapid phase I and II biotransformation, leading to short half-lives and limited tissue exposure [8].

Physicochemical parameters such as polar surface area and hydrogen bonding density have been shown to critically influence oral absorption and tissue penetration [9]. Accordingly, early stage triaging of AA scaffolds should integrate PK profiling, microsomal stability, and toxicity screening to eliminate candidates unlikely to achieve therapeutic exposure, even when cellular potency appears promising[41].

6.2 Indications for chemical optimization

Chemical optimization should be pursued only when a scaffold demonstrates a viable balance between intrinsic potency and modifiable ADME liabilities. Structure–activity relationship studies across lycorine, crinine, haemanthamine, and narciclasine-type alkaloids consistently reveal tight stereochemical and functional group constraints, where minor perturbations often abolish biological activity[2].

Successful medicinal chemistry efforts have therefore focused on limited, exposure oriented modifications, such as modulation of lipophilicity or metabolic hotspots, rather than extensive scaffold remodelling [61]. In cases where activity is inseparable from highly polar or metabolically labile motifs, further chemical optimization frequently results in non-productive analogue series with diminished efficacy [10]. These observations highlight the importance of early decisions based on SAR tractability rather than synthetic feasibility alone.

6.3 Indications for Drug Delivery Technologies

Nano-enabled delivery approaches become strategically relevant only when chemical optimization reaches intrinsic limits, yet the parent alkaloid retains compelling mechanistic relevance. Nanocarrier systems including polymeric matrices, liposomes, and stimulus responsive platforms have demonstrated the ability to enhance circulation time, protect labile natural products, and improve tumour accumulation [57].

For Amaryllidaceae alkaloids, controlled release formulations of narciclasine illustrate how nano-delivery can partially overcome exposure limitations without altering the pharmacophore [13]. More advanced designs exploiting pH, redox, or enzyme responsive triggers further improve tumour selective release [62]. Nevertheless, nano delivery should be viewed as a complementary strategy, not a rescue solution for fundamentally unsuitable scaffolds [7].

6.4 Criteria for scaffold triage

An essential yet underutilized component of translation driven discovery is the deliberate abandonment of non-viable scaffolds. Alkaloids exhibiting irreversible toxicity, extreme PK instability, or unmodifiable SAR constraints should be deprioritized, regardless of in vitro potency [34].

Historical experience across anticancer drug development demonstrates that persistence with exposure-incompatible chemotypes leads to fragmented optimization efforts and resource dilution [35]. For Amaryllidaceae alkaloids, rational discontinuation criteria based on PK failure, toxicity margins, and delivery feasibility are therefore as critical as lead advancement decisions. Embedding such criteria within early development workflows ensures that translational resources are focused on scaffolds with a realistic probability of clinical success.

7. Conclusions

Amaryllidaceae alkaloids embody a persistent paradox in anticancer drug discovery, pronounced molecular potency coupled with chemical and biological features that systematically undermine clinical translation. Accumulating evidence indicates that these limitations are not incidental but arise from chemotype-specific constraints that recur across optimization efforts. Progress in this area therefore depends on moving beyond potency-driven exploration toward early, translation aware decision making, where SAR rigidity, stereochemical sensitivity, exposure limitations, and mechanism linked toxicity are evaluated in parallel rather than sequentially. Such an approach enables informed differentiation between scaffolds that merit chemical optimization, those better addressed through formulation strategies, and those that warrant early triage. Within this framework, nano-enabled delivery emerges as a context-dependent tool whose impact is governed by the underlying pharmacophore and biological mechanism, rather than as a universal remedy. Strategic deployment of delivery technologies, combined with rational chemical modification and early PK toxicity integration, offers a more realistic pathway to extending therapeutic windows. More broadly, these considerations highlight a shift in how natural product derived anticancer agents may be advanced, prioritizing feasibility, selectivity, and exposure early can reduce late-stage attrition and focus resources on candidates with genuine translational promise. Applied consistently, this perspective has the potential to recalibrate discovery pipelines not only for Amaryllidaceae alkaloids, but for structurally complex natural products more generally.

References

[1] R. Watkins, L. Wu, C. Zhang, R. M. Davis, et B. Xu, « Natural product-based nanomedicine: recent advances and issues », *Int. J. Nanomedicine*, vol. 10, p. 6055-6074, 2015, doi: 10.2147/IJN.S92162.

[2] J. C. Cedrón, Á. G. Ravelo, L. G. León, J. M. Padrón, et A. Estévez-Braun, « Antiproliferative and Structure Activity Relationships of Amaryllidaceae Alkaloids », *Mol. Basel Switz.*, vol. 20, n° 8, p. 13854-13863, juill. 2015, doi: 10.3390/molecules200813854.

[3] M. J. Martins De Paiva *et al.*, « Antitumor evaluation of amaryllidaceae alkaloids on cancer cell lines: A literature review », *Electron. J. Gen. Med.*, vol. 21, n° 1, p. em562, janv. 2024, doi: 10.29333/ejgm/14040.

[4] Y. Ding *et al.*, « Phytochemical and biological investigations of Amaryllidaceae alkaloids: a review », *J. Asian Nat. Prod. Res.*, vol. 19, n° 1, p. 53-100, janv. 2017, doi: 10.1080/10286020.2016.1198332.

[5] Y.-M. Zhang *et al.*, « Uncover the anticancer potential of lycorine », *Chin. Med.*, vol. 19, n° 1, p. 121, sept. 2024, doi: 10.1186/s13020-024-00989-9.

[6] J. J. Nair, J. van Staden, et J. Bastida, « Apoptosis-Inducing Effects of Amaryllidaceae Alkaloids », *Curr. Med. Chem.*, vol. 23, n° 2, p. 161-185, janv. 2016, doi: 10.2174/0929867323666151118121124.

[7] D. V. Bhalani, B. Nutan, A. Kumar, et A. K. Singh Chandel, « Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics », *Biomedicines*, vol. 10, n° 9, p. 2055, août 2022, doi: 10.3390/biomedicines10092055.

[8] S. Jahn, B. Seiwert, S. Kretzing, G. Abraham, R. Regenthal, et U. Karst, « Metabolic studies of the Amaryllidaceous alkaloids galantamine and lycorine based on electrochemical simulation in addition to in vivo and in vitro models », *Anal. Chim. Acta*, vol. 756, p. 60-72, 2012, Consulté le: 10 décembre 2025. [En ligne]. Disponible sur: https://www.sciencedirect.com/science/article/pii/S0003267012015644

[9] J. Kelder, P. D. Grootenhuis, D. M. Bayada, L. P. Delbressine, et J. P. Ploemen, « Polar molecular surface as a dominating determinant for oral absorption and brain penetration of drugs », *Pharm. Res.*, vol. 16, n° 10, p. 1514-1519, oct. 1999, doi: 10.1023/a:1015040217741.

[10]L. Ingrassia *et al.*, « Structure−Activity Relationship Analysis of Novel Derivatives of Narciclasine (an Amaryllidaceae Isocarbostyril Derivative) as Potential Anticancer Agents », *J. Med. Chem.*, vol. 52, n° 4, p. 1100-1114, févr. 2009, doi: 10.1021/jm8013585.

[11]L. Cahlíková, I. Kawano, M. Řezáčová, G. Blunden, D. Hulcová, et R. Havelek, « The Amaryllidaceae alkaloids haemanthamine, haemanthidine and their semisynthetic derivatives as potential drugs », *Phytochem. Rev.*, vol. 20, n° 1, p. 303-323, févr. 2021, doi: 10.1007/s11101-020-09675-8.

[12]J. Yang *et al.*, « Nanotechnology-Based Drug Delivery Systems for Honokiol: Enhancing Therapeutic Potential and Overcoming Limitations », *Int. J. Nanomedicine*, vol. 18, p. 6639-6665, 2023, doi: 10.2147/IJN.S431409.

[13]F. M. Veronese *et al.*, « In vitro and in vivo behaviour of narciclasine released from matrices based on poly (2-hydroxyethyl methacrylate) », *Farm. Soc. Chim. Ital. 1989*, vol. 46, n° 9, p. 1061-1070, sept. 1991.

[14]Z. Jin, « Amaryllidaceae and Sceletium alkaloids », *Nat. Prod. Rep.*, vol. 26, n° 3, p. 363-381, mars 2009, doi: 10.1039/b718044f.

[15]A. S. Kireev *et al.*, « Synthesis and biological evaluation of aromatic analogues of conduritol F, L-chiro-inositol, and dihydroconduritol F structurally related to the amaryllidaceae anticancer constituents », *J. Org. Chem.*, vol. 71, n° 15, p. 5694-5707, juill. 2006, doi: 10.1021/jo0607562.

[16]H. Maeda et N. Dudareva, « The shikimate pathway and aromatic amino Acid biosynthesis in plants », *Annu. Rev. Plant Biol.*, vol. 63, p. 73-105, 2012, doi: 10.1146/annurev-arplant-042811-105439.

[17]« Chemodiversity, chemotaxonomy and chemoecology of Amaryllidaceae alkaloids », in *The Alkaloids: Chemistry and Biology*, vol. 83, Academic Press, 2020, p. 113-185. doi: 10.1016/bs.alkal.2019.10.002.

[18]« Frontiers | Functional characterization of CYP96T1-like cytochrome P450 from Lycoris aurea catalyzing para-para′ and para-ortho′ oxidative coupling in Amaryllidaceae alkaloids biosynthesis ». Consulté le: 17 décembre 2025. [En ligne]. Disponible sur: https://www.frontiersin.org/journals/plant-science/articles/10.3389/fpls.2024.1438102/full

[19]L. R. Tallini *et al.*, « Chemical Survey of Three Species of the Genus Rauhia Traub (Amaryllidaceae) », *Plants Basel Switz.*, vol. 11, n° 24, p. 3549, déc. 2022, doi: 10.3390/plants11243549.

[20]D. Lamoral-Theys *et al.*, « Lycorine, the Main Phenanthridine Amaryllidaceae Alkaloid, Exhibits Significant Antitumor Activity in Cancer Cells That Display Resistance to Proapoptotic Stimuli: An Investigation of Structure−Activity Relationship and Mechanistic Insight », *J. Med. Chem.*, vol. 52, n° 20, p. 6244-6256, oct. 2009, doi: 10.1021/jm901031h.

[21]Y.-M. Zhang *et al.*, « Uncover the anticancer potential of lycorine », *Chin. Med.*, vol. 19, n° 1, p. 121, sept. 2024, doi: 10.1186/s13020-024-00989-9.

[22]X.-D. Zuo, S.-M. Guo, R. Yang, J.-H. Xie, et Q.-L. Zhou, « Bioinspired enantioselective synthesis of crinine-type alkaloids via iridium-catalyzed asymmetric hydrogenation of enones », *Chem. Sci.*, vol. 8, n° 9, p. 6202-6206, sept. 2017, doi: 10.1039/c7sc02112g.

[23]J. P. de Andrade *et al.*, « Crinine-type alkaloids from Hippeastrum aulicum and H. calyptratum », *Phytochemistry*, vol. 103, p. 188-195, juill. 2014, doi: 10.1016/j.phytochem.2014.03.007.

[24]G. Luchetti *et al.*, « Bulbispermine: A Crinine-Type Amaryllidaceae Alkaloid Exhibiting Cytostatic Activity toward Apoptosis-Resistant Glioma Cells », *ChemMedChem*, vol. 7, n° 5, p. 815-822, 2012, doi: 10.1002/cmdc.201100608.

[25]S. Pellegrino *et al.*, « The Amaryllidaceae Alkaloid Haemanthamine Binds the Eukaryotic Ribosome to Repress Cancer Cell Growth », *Struct. Lond. Engl. 1993*, vol. 26, n° 3, p. 416-425.e4, mars 2018, doi: 10.1016/j.str.2018.01.009.

[26]A. Kornienko et A. Evidente, « Chemistry, biology, and medicinal potential of narciclasine and its congeners », *Chem. Rev.*, vol. 108, n° 6, p. 1982-2014, juin 2008, doi: 10.1021/cr078198u.

[27]J. J. Nair et J. van Staden, « Antiviral alkaloid principles of the plant family Amaryllidaceae », *Phytomedicine Int. J. Phytother. Phytopharm.*, vol. 108, p. 154480, janv. 2023, doi: 10.1016/j.phymed.2022.154480.

[28]G. S. J. Mannens *et al.*, « The metabolism and excretion of galantamine in rats, dogs, and humans », *Drug Metab. Dispos. Biol. Fate Chem.*, vol. 30, n° 5, p. 553-563, mai 2002, doi: 10.1124/dmd.30.5.553.

[29]A. Baez et D. Vazquez, « Binding of [3H]narciclasine to eukaryotic ribosomes A study on a structure-activity relationship », *Biochim. Biophys. Acta BBA - Nucleic Acids Protein Synth.*, vol. 518, n° 1, p. 95-103, mars 1978, doi: 10.1016/0005-2787(78)90119-3.

[30]M.-K. Shieu *et al.*, « Narciclasine suppresses oral cancer metastasis by modulating cathepsin B and extracellular signal-related kinase pathways », *Biomed. Pharmacother. Biomedecine Pharmacother.*, vol. 158, p. 114159, févr. 2023, doi: 10.1016/j.biopha.2022.114159.

[31]Y. Qiu *et al.*, « Narciclasine suppresses esophageal cancer cell proliferation and migration by inhibiting the FAK signaling pathway », *Eur. J. Pharmacol.*, vol. 921, p. 174669, avr. 2022, doi: 10.1016/j.ejphar.2021.174669.

[32]R. Gopalakrishnan, H. Matta, S. Choi, et P. M. Chaudhary, « Narciclasine, an isocarbostyril alkaloid, has preferential activity against primary effusion lymphoma », *Sci. Rep.*, vol. 10, n° 1, p. 5712, mars 2020, doi: 10.1038/s41598-020-62690-9.

[33]J. J. Nair et J. Van Staden, « Cytotoxic lycorine alkaloids of the plant family Amaryllidaceae », *Bioorganic Chem.*, vol. 163, p. 108619, août 2025, doi: 10.1016/j.bioorg.2025.108619.

[34]L. Sommerová, E. Michalová, et R. Hrstka, « [New Approaches for Chemosensitivity Testing in Malignant Diseases] », *Klin. Onkol. Cas. Ceske Slov. Onkol. Spolecnosti*, vol. 31, n° 2, p. 117-124, 2018, doi: 10.14735/amko2018117.

[35]J. H. Goldie, « Drug resistance and cancer chemotherapy strategy in breast cancer », *Breast Cancer Res. Treat.*, vol. 3, n° 2, p. 129-136, juin 1983, doi: 10.1007/BF01803555.

[36]D. Liu *et al.*, « Total synthesis of lycorine-type alkaloids by cyclopropyl ring-opening rearrangement », *Org. Biomol. Chem.*, vol. 12, n° 20, p. 3191-3200, mai 2014, doi: 10.1039/c4ob00126e.

[37]S. Vshyvenko, M. R. Reisenauer, S. Rogelj, et T. Hudlicky, « Synthesis and biological evaluation of unnatural derivatives of narciclasine: 7-aza-nornarciclasine and its N-oxide », *Bioorg. Med. Chem. Lett.*, vol. 24, n° 17, p. 4236-4238, sept. 2014, doi: 10.1016/j.bmcl.2014.07.034.

[38]L. Carrasco, M. Fresno, et D. Vazquez, « Narciclasine: an antitumour alkaloid which blocks peptide bond formation by eukaryotic ribosomes », *FEBS Lett.*, vol. 52, n° 2, p. 236-239, avr. 1975, doi: 10.1016/0014-5793(75)80813-1.

[39]E. R. Cole *et al.*, « Cytotoxic and Genotoxic Activities of Alkaloids from the Bulbs of Griffinia gardneriana and Habranthus itaobinus (Amaryllidaceae) », *Anticancer Agents Med. Chem.*, vol. 19, n° 5, p. 707-717, mars 2019, doi: 10.2174/1871520619666190118122523.

[40]L. Ren, H. Zhao, et Z. Chen, « Study on pharmacokinetic and tissue distribution of lycorine in mice plasma and tissues by liquid chromatography-mass spectrometry », *Talanta*, vol. 119, p. 401-406, févr. 2014, doi: 10.1016/j.talanta.2013.11.014.

[41]M. J. M. Paiva, G. N. L. Nascimento, I. a. M. Damasceno, T. T. Santos, et D. Silveira, « Pharmacological and toxicological effects of Amaryllidaceae », *Braz. J. Biol. Rev. Brasleira Biol.*, vol. 83, p. e277092, 2023, doi: 10.1590/1519-6984.277092.

[42]A. L. Harvey, « The pharmacology of galanthamine and its analogues », *Pharmacol. Ther.*, vol. 68, n° 1, p. 113-128, 1995, doi: 10.1016/0163-7258(95)02002-0.

[43]C. Lv *et al.*, « Narciclasine targets STAT3 via distinct mechanisms in tamoxifen-resistant breast cancer cells », *Mol. Ther. Oncolytics*, vol. 24, p. 340-354, mars 2022, doi: 10.1016/j.omto.2021.12.025.

[44]M. Roy, L. Liang, X. Xiao, P. Feng, M. Ye, et J. Liu, « Lycorine: A prospective natural lead for anticancer drug discovery », *Biomed. Pharmacother. Biomedecine Pharmacother.*, vol. 107, p. 615-624, nov. 2018, doi: 10.1016/j.biopha.2018.07.147.

[45]T. G. Adessi *et al.*, « Clinanthus microstephium, an Amaryllidaceae Species with Cholinesterase Inhibitor Alkaloids: Structure-Activity Analysis of Haemanthamine Skeleton Derivatives », *Chem. Biodivers.*, vol. 16, n° 5, p. e1800662, mai 2019, doi: 10.1002/cbdv.201800662.

[46]S. Ka *et al.*, « Gigantelline, gigantellinine and gigancrinine, cherylline- and crinine-type alkaloids isolated from Crinum jagus with anti-acetylcholinesterase activity », *Phytochemistry*, vol. 175, p. 112390, juill. 2020, doi: 10.1016/j.phytochem.2020.112390.

[47]J. Goulart Stollmaier *et al.*, « Conversion of Natural Narciclasine to Its C-1 and C-6 Derivatives and Their Antitumor Activity Evaluation: Some Unusual Chemistry of Narciclasine », *Mol. Basel Switz.*, vol. 27, n° 13, p. 4141, juin 2022, doi: 10.3390/molecules27134141.

[48]P. Dumont *et al.*, « The Amaryllidaceae Isocarbostyril Narciclasine Induces Apoptosis By Activation of the Death Receptor and/or Mitochondrial Pathways in Cancer Cells But Not in Normal Fibroblasts », *Neoplasia*, vol. 9, n° 9, p. 766-776, sept. 2007, doi: 10.1593/neo.07535.

[49]R. Bachus, U. Bickel, T. Thomsen, I. Roots, et H. Kewitz, « The O-demethylation of the antidementia drug galanthamine is catalysed by cytochrome P450 2D6 », *Pharmacogenet. Genomics*, vol. 9, n° 6, p. 661, déc. 1999, Consulté le: 6 décembre 2025. [En ligne]. Disponible sur: https://journals.lww.com/jpharmacogenetics/abstract/1999/12000/The_O_demethylation_of_the_antidementia_drug.1.aspx

[50]G. Stork et D. J. M. Jr, « A simple, stereospecific synthesis of the skeleton of the lycorine alkaloids », ACS Publications. Consulté le: 10 décembre 2025. [En ligne]. Disponible sur: https://pubs.acs.org/doi/pdf/10.1021/ja00517a075

[51]J. McNulty *et al.*, « Truncated ring-A amaryllidaceae alkaloid modulates the host cell integrated stress response, exhibiting antiviral activity to HSV-1 and SARSCoV-2 », *Sci. Rep.*, vol. 13, n° 1, p. 1639, janv. 2023, doi: 10.1038/s41598-023-28691-0.

[52]J.-M. Sabatier, « Special Issue “Structure-Activity Relationship of Natural Products” », *Mol. Basel Switz.*, vol. 22, n° 5, p. 697, avr. 2017, doi: 10.3390/molecules22050697.

[53]M. Heinrich, « Galanthamine from Galanthus and other Amaryllidaceae--chemistry and biology based on traditional use », *Alkaloids Chem. Biol.*, vol. 68, p. 157-165, 2010, doi: 10.1016/s1099-4831(10)06804-5.

[54]S. Wang, Y. Chen, J. Guo, et Q. Huang, « Liposomes for Tumor Targeted Therapy: A Review », *Int. J. Mol. Sci.*, vol. 24, n° 3, p. 2643, janv. 2023, doi: 10.3390/ijms24032643.

[55]M. A. Abd el Hafiz, M. A. Ramadan, M. L. Jung, J. P. Beck, et R. Anton, « Cytotoxic activity of Amaryllidaceae alkaloids from Crinum augustum and Crinum bulbispermum », *Planta Med.*, vol. 57, n° 5, p. 437-439, oct. 1991, doi: 10.1055/s-2006-960144.

[56]S. Henry *et al.*, « 5,10b-Ethanophenanthridine amaryllidaceae alkaloids inspire the discovery of novel bicyclic ring systems with activity against drug resistant cancer cells », *Eur. J. Med. Chem.*, vol. 120, p. 313-328, sept. 2016, doi: 10.1016/j.ejmech.2016.05.004.

[57]R. Watkins, L. Wu, C. Zhang, R. M. Davis, et B. Xu, « Natural product-based nanomedicine: recent advances and issues », *Int. J. Nanomedicine*, vol. 10, p. 6055-6074, sept. 2015, doi: 10.2147/IJN.S92162.

[58]Y. Wu, L. He, S. Zhao, Y. Jiang, Z. Yang, et X. Deng, « Tumor microenvironment pH-responsive size-transformable peptide self-assembling nanocarriers for tumor-specific treatment », *Biomater. Adv.*, vol. 173, p. 214293, août 2025, doi: 10.1016/j.bioadv.2025.214293.

[59]X. Ling *et al.*, « Glutathione-Responsive Prodrug Nanoparticles for Effective Drug Delivery and Cancer Therapy », *ACS Nano*, vol. 13, n° 1, p. 357-370, janv. 2019, doi: 10.1021/acsnano.8b06400.

[60]Y. Mi *et al.*, « Enzyme-responsive multistage vector for drug delivery to tumor tissue », *Pharmacol. Res.*, vol. 113, n° Pt A, p. 92-99, nov. 2016, doi: 10.1016/j.phrs.2016.08.024.

[61]Y.-H. Wang, Q.-L. Wan, C.-D. Gu, H.-R. Luo, et C.-L. Long, « Synthesis and biological evaluation of lycorine derivatives as dual inhibitors of humanacetylcholinesterase and butyrylcholinesterase », *Chem. Cent. J.*, vol. 6, n° 1, p. 96, sept. 2012, doi:.1186/1752-153X-6-96.

[62]Y. Liu *et al.*, « Design of pH-Responsive Nanomaterials Based on the Tumor Microenvironment », *Int. J. Nanomedicine*, vol. 20, p. 705-721, 2025, doi: 10.2147/IJN.S504629.