

REVIEW ARTICLE

Plant-derived alkaloids at the interface of cancer biology and translational pharmacology: Mechanisms, experimental evidence, and clinical challenges

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Abstract

Cancer remains a major global health burden driven by complex molecular alterations that challenge current therapeutic strategies. Plant-derived alkaloids, characterized by remarkable structural diversity and multitarget biological activity, have emerged as promising candidates in anticancer drug discovery; however, despite substantial preclinical evidence, their clinical translation remains limited. This review synthesizes current knowledge on the molecular mechanisms underlying the anticancer effects of these compounds, including modulation of microtubule dynamics, induction of apoptosis, DNA damage, and regulation of oncogenic signaling pathways such as PI3K/Akt/mTOR and NF-κB. Evidence from *in vitro* and *in vivo* studies is critically examined, highlighting both potent cytotoxic activity and variability in pharmacological responses, while distinguishing mechanistic causality from associative observations in light of experimental design limitations, particularly the predominance of *in vitro* models and lack of standardized methodologies. Key translational barriers are further discussed, including toxicity, pharmacokinetic instability, and the limited predictive value of current preclinical models. In this context, we propose that integrating mechanistic pharmacology with innovative translational frameworks is essential to enhance the clinical applicability of alkaloid-based therapies. Collectively, these insights reinforce the potential of plant-derived alkaloids as multitarget anticancer agents and underscore the need for integrative strategies to bridge the gap between experimental efficacy and clinical application.

Keywords: Amaryllidaceae alkaloids; Anticancer natural products; Translational oncology; Zebrafish cancer models; Drug discovery; Ribosomal inhibition

1. Introduction

Cancer is a biologically complex and heterogeneous disease characterized by dynamic molecular adaptations that challenge therapeutic efficacy. Despite advances in targeted therapies and immunomodulation, treatment failure remains frequent due to resistance mechanisms, systemic toxicity, and tumor plasticity. Despite significant advances in targeted therapies, immunotherapy, and precision medicine, the clinical management of cancer continues to be limited by therapeutic resistance, systemic toxicity, and high economic burden.^{1,2} These challenges highlight the urgent need for the identification and development of novel pharmacological agents capable of modulating complex oncogenic pathways. This resistance is frequently driven by dynamic genetic and epigenetic adaptations, reinforcing the need for pharmacological agents capable of modulating multiple cellular pathways simultaneously rather than single molecular targets.³⁻⁵

Natural products have historically played a fundamental role in anticancer drug discovery, serving both as direct therapeutic agents and as structural templates for semisynthetic derivatives. Among these, plant-derived alkaloids constitute a particularly important class of bioactive compounds due to their remarkable structural diversity and wide range of biological activities.³ Their multitarget pharmacological profile enables simultaneous modulation of multiple signaling pathways involved in tumor growth, survival, and metastasis, which may be advantageous in addressing tumor heterogeneity and adaptive resistance mechanisms.

Over the past decades, numerous studies have demonstrated the anticancer potential of plant-derived alkaloids across various experimental models. These compounds exert their effects through diverse mechanisms, including disruption of microtubule dynamics, induction of apoptosis, interference with DNA replication, and modulation of key oncogenic signaling pathways such as PI3K/Akt/mTOR and nuclear factor- κ B.^{4,5} However, despite this substantial body of preclinical evidence, the translation of these compounds into clinically effective therapies remains limited.

This translational gap reflects several critical limitations, including pharmacokinetic instability, narrow therapeutic windows, and insufficient predictive preclinical models. In addition, the predominance of *in vitro* studies and the lack of standardized experimental approaches further compromise the reliability and comparability of existing data.⁶ These challenges underscore the need for integrative research strategies that combine mechanistic understanding with robust *in vivo* validation.

In this context, this review aims to provide a comprehensive and critical synthesis of the current evidence on plant-derived alkaloids in cancer therapy. We examine their molecular mechanisms of action, evaluate their experimental efficacy, and analyze the major methodological limitations and translational barriers that hinder their clinical development. By integrating mechanistic insights with translational perspectives, we seek to contribute to the rational development of alkaloid-based strategies in oncology.

To further contextualize the current research landscape, a bibliometric analysis based on keyword co-occurrence was performed using data retrieved from PubMed and visualized with VOSviewer. This approach enables the identification of major thematic clusters and emerging research trends in the field of plant-derived alkaloids and cancer. The analysis revealed a highly interconnected network structured around four main domains: molecular mechanisms of action, including apoptosis and oxidative stress; intracellular signaling pathways involved in tumor progression; drug resistance mechanisms and tumor microenvironment interactions; and nanotechnology-based drug delivery systems. These findings highlight the multidimensional nature of alkaloid-based anticancer research and reinforce the importance of integrative approaches in the development of novel therapeutic strategies (Figure 1).

To ensure transparency and reproducibility, the methodological parameters used for the bibliometric analysis are described below. The analysis was conducted using PubMed as the primary database. The search strategy included the terms (“alkaloids” AND “cancer” AND “anticancer”) applied to titles and abstracts. Articles published between 2000 and 2025 were considered. Duplicate records and non-relevant studies were excluded. The final dataset was exported in RIS format and analyzed using VOSviewer (version 1.6.20). A minimum keyword occurrence threshold of 15 was applied, and co-occurrence analysis was performed using the full counting method to generate the network visualization.

Unlike recent reviews that primarily compile the anticancer activity of plant-derived alkaloids, this work adopts a critical and integrative perspective that connects mechanistic pharmacology with translational limitations. While previous studies have focused on describing biological activity, they often overlook the impact of methodological heterogeneity, pharmacokinetic constraints, and experimental bias on the reliability of reported outcomes. By explicitly addressing these factors, the present review provides a more realistic assessment of the challenges involved in translating preclinical findings into clinically relevant applications.

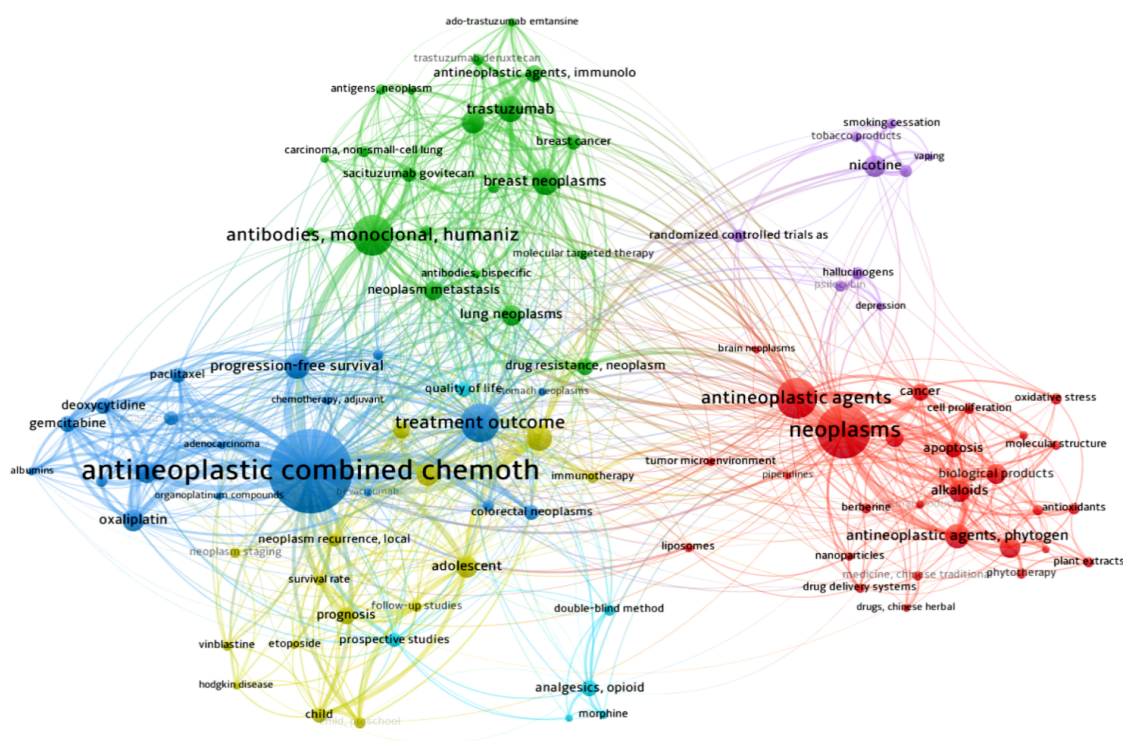


Figure 1. Keyword co-occurrence network generated using VOSviewer (version 1.6.20) from PubMed-indexed studies on plant-derived alkaloids in cancer research. Node size represents keyword frequency, and link strength indicates co-occurrence relationships. Clustering analysis identified major thematic domains, including apoptosis, signaling pathways, drug resistance, and nanotechnology-based delivery systems. The visualization was produced by the authors. Based on these insights, the following sections provide a detailed analysis of the molecular mechanisms, pharmacological properties, and translational potential of plant-derived alkaloids in cancer therapy.

2. Mechanistic insights and experimental evidence of plant-derived alkaloids

2.1. Multitarget mechanisms in cancer biology

Plant-based alkaloids demonstrate anticancer properties by engaging a complex array of molecular interactions, owing to their structural variety and evolutionary refinement. Unlike traditional chemotherapies targeting a single pathway, these compounds influence multiple cellular mechanisms at once, offering potential benefits in overcoming tumor diversity and resistance to treatment. For example, berberine simultaneously modulates ROS generation, Bcl-2 family proteins, and NF- κ B signaling, while lycorine interferes with protein synthesis and cell cycle progression.

One of the most extensively characterized mechanisms involves the disruption of microtubule dynamics, leading to mitotic arrest and inhibition of cell proliferation. Alkaloids such as vincristine interfere with tubulin polymerization, impairing mitotic spindle formation and inducing cell cycle arrest at the G2/M phase.⁷ This mechanism has been

widely validated and remains a cornerstone of anticancer pharmacology. At the molecular level, this disruption results in spindle assembly checkpoint activation, prolonged mitotic arrest, and subsequent apoptotic signaling, highlighting the vulnerability of rapidly proliferating tumor cells to cytoskeletal perturbations.

In addition to cytoskeletal disruption, apoptosis induction represents a central mechanism underlying the anticancer activity of many alkaloids. These compounds activate both intrinsic and extrinsic apoptotic pathways through mitochondrial dysfunction, caspase activation, and modulation of key regulatory proteins, including Bax, Bcl-2, and PARP.⁸ Importantly, some alkaloids demonstrate the ability to overcome apoptosis resistance, which is a hallmark of advanced and treatment-refractory tumors. These apoptotic effects are often mediated by mitochondrial membrane depolarization and reactive oxygen species accumulation, which act as upstream triggers for caspase activation and DNA fragmentation.

Alkaloids also modulate critical oncogenic signaling pathways that regulate tumor progression. These include

PI3K/Akt/mTOR, NF- κ B, and MAPK pathways, which are essential for cell survival, proliferation, and angiogenesis.⁹ Inhibition of these pathways results in reduced tumor growth and metastatic potential, highlighting the multitarget nature of these compounds.

Another important mechanism involves DNA damage and interference with DNA repair processes. Camptothecin-derived alkaloids stabilize DNA-topoisomerase complexes, preventing DNA religation and leading to the accumulation of DNA strand breaks.¹⁰ This mechanism ultimately triggers cell death and has been exploited in several clinically relevant anticancer agents.

Furthermore, emerging evidence indicates that plant-derived alkaloids can induce alternative forms of cell death, including autophagy, necroptosis, and cellular senescence, particularly in apoptosis-resistant cancer cells.¹¹ The multitarget mechanisms of alkaloids in cancer therapy are summarized in Figure 2. These findings highlight the potential of alkaloids as multitarget agents capable of overcoming drug resistance and improving therapeutic outcomes.

2.2. Experimental evidence: *In vitro* and *in vivo* activity

The experimental evidence supporting the anticancer potential of plant-derived alkaloids is extensive, although heterogeneous in design and quality. *In vitro* studies represent the majority of available data and consistently demonstrate cytotoxic effects across a wide range of cancer cell lines. Several alkaloids exhibit high potency, with nanomolar IC₅₀ values, indicating strong antiproliferative activity.¹² Compounds such as narciclasine and conofolidine exemplify this high potency, while others display moderate

activity but improved selectivity profiles.¹³

In addition to cytotoxicity, *in vitro* studies demonstrate that alkaloids can induce cell cycle arrest, inhibit proliferation, and activate programmed cell death pathways. However, the magnitude of these effects is highly dependent on experimental conditions, including concentration, exposure time, and cancer type, which complicates direct comparison between studies.¹⁴

In contrast, *in vivo* evidence remains comparatively limited but provides important insights into the translational potential of these compounds. Several alkaloids have demonstrated significant tumor growth inhibition in animal models, including xenograft systems, where reductions in tumor volume and improved survival outcomes have been observed.¹⁵ These findings support the biological relevance of alkaloid activity beyond simplified cellular systems.

Nevertheless, *in vivo* efficacy is frequently constrained by pharmacokinetic limitations, including poor bioavailability, rapid metabolism, and limited tissue distribution.¹⁶ These factors contribute to reduced therapeutic effectiveness and highlight the need for improved drug delivery strategies.

2.3. Methodological limitations

Although the available experimental data indicate relevant anticancer activity, important methodological constraints compromise both the robustness and reproducibility of these findings. One of the most significant limitations is the disproportionate reliance on *in vitro* models, with comparatively limited *in vivo* validation and scarce clinical evidence.¹⁷ This imbalance weakens the translational relevance of the reported effects.

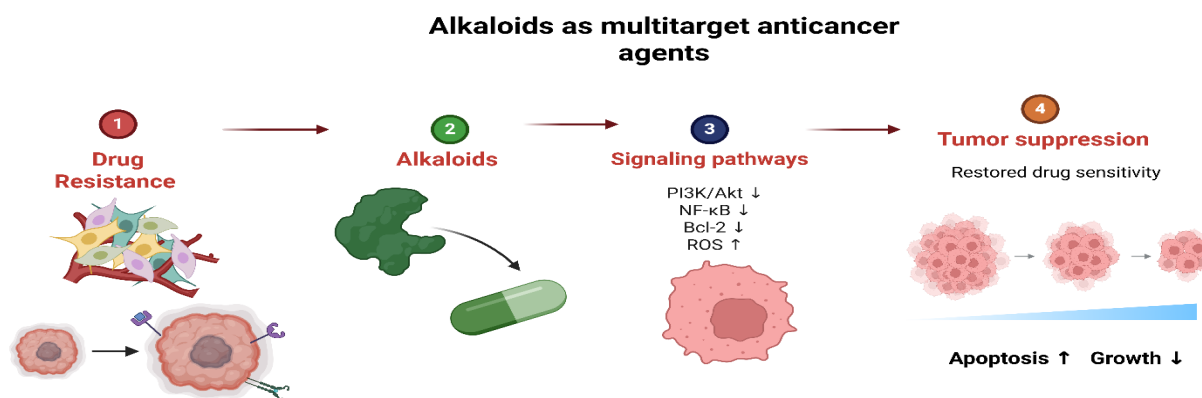


Figure 2. Alkaloids as multitarget anticancer agents. Alkaloids overcome drug resistance by modulating key oncogenic signaling pathways, including PI3K/Akt, NF- κ B, and Bcl-2, while increasing reactive oxygen species (ROS) production. These effects lead to apoptosis induction and suppression of tumor growth. Schematic created by the authors using BioRender.com. Jhuly, M. (2026) <https://BioRender.com/q52ne5w>

Furthermore, a substantial number of studies are based on single-endpoint assays, particularly cell viability measurements, without adequate mechanistic investigation. Such an approach restricts the ability to establish clear causal relationships between observed biological responses and the molecular pathways involved.¹⁸

In addition, the absence of standardized experimental protocols represents a critical barrier to data interpretation. Differences in assay conditions—including variations in compound concentration, exposure duration, and the choice of cellular models—introduce heterogeneity that hinders cross-study comparison and contributes to inconsistencies in reported outcomes.¹⁹ Moreover, toxicity and selectivity are often insufficiently evaluated, despite their central importance in drug development. The absence of systematic toxicity profiling represents a significant gap in the current literature.²⁰

To overcome these limitations, future studies should prioritize the adoption of more physiologically relevant experimental models, such as three-dimensional (3D) cultures, organoids, and patient-derived xenografts, which better recapitulate tumor complexity and microenvironmental interactions. In parallel, the implementation of standardized experimental protocols—including harmonized concentration ranges, exposure times, and reporting criteria—would significantly improve reproducibility and comparability across studies.

From a translational perspective, integrating pharmacokinetic and pharmacodynamic evaluations early in the experimental design is essential to better predict *in vivo* behavior. In addition, the use of advanced drug delivery systems, particularly nanotechnology-based approaches, may enhance bioavailability and reduce discrepancies between experimental and clinical outcomes. Collectively, these strategies may help bridge the gap between experimental efficacy and clinical applicability in alkaloid-based anticancer research.

2.4. Translational implications

The collective evidence indicates that plant-derived alkaloids possess substantial anticancer potential; however, their clinical translation remains limited. This discrepancy reflects a fundamental disconnect between preclinical efficacy and clinical applicability.²¹

Key barriers to translation include systemic toxicity, narrow therapeutic windows, and pharmacokinetic instability. In addition, the lack of predictive preclinical models further hinders the identification of compounds with true clinical potential.²²

Importantly, the multitarget nature of alkaloids,

while advantageous from a mechanistic perspective, also introduces complexity in optimizing therapeutic profiles. Balancing efficacy and safety remains a major challenge in the development of alkaloid-based therapies.²³

Taken together, these findings suggest that the primary limitation of alkaloid-based anticancer strategies lies not in insufficient biological activity, but in the challenges associated with translating this activity into clinically viable interventions.²⁴

3. Chemical diversity and structure–activity relationships of plant-derived alkaloids

3.1. Structural diversity of alkaloids

Plant-derived alkaloids comprise a structurally diverse class of nitrogen-containing secondary metabolites, which can be broadly classified into several groups, including isoquinoline, indole, quinoline, and Amaryllidaceae alkaloids. This structural diversity is a key determinant of their wide range of biological activities, particularly in the context of anticancer pharmacology.²⁵

Isoquinoline alkaloids, such as berberine and sanguinarine, are among the most extensively studied due to their ability to intercalate with DNA and modulate key signaling pathways involved in cell proliferation and apoptosis.²⁶ In contrast, indole alkaloids, including vincristine and vinblastine, primarily exert their anticancer effects through disruption of microtubule dynamics, highlighting the relationship between chemical structure and biological function.²⁷

Amaryllidaceae alkaloids, such as lycorine and narciclasine, represent a unique subclass characterized by distinct ring systems and potent biological activity. These compounds have been shown to interfere with protein synthesis and ribosomal function, distinguishing them mechanistically from other alkaloid classes.²⁸

The structural complexity of these molecules not only contributes to their biological activity but also presents challenges for large-scale synthesis and optimization, which can limit their translational development.²⁹

3.2. Structure–activity relationships

Structure–activity relationship (SAR) studies have provided important insights into the molecular determinants of anticancer activity among plant-derived alkaloids. Small modifications in functional groups, stereochemistry, and ring systems can significantly alter biological potency, selectivity, and toxicity profiles.³⁰

For example, substitutions in the isoquinoline backbone of berberine derivatives have been shown to

enhance cytotoxic activity by increasing cellular uptake and interaction with intracellular targets.³¹ Similarly, modifications in the indole ring system of vinca alkaloids can influence their binding affinity to tubulin, thereby affecting their ability to disrupt mitotic processes.³²

In Amaryllidaceae alkaloids, structural features such as hydroxylation patterns and ring conformation play a critical role in modulating biological activity. Narciclasine derivatives, for instance, exhibit high potency due to their ability to interact with ribosomal subunits, and even minor structural changes can result in significant loss of activity.³³ These findings underscore the importance of precise structural optimization in the development of alkaloid-based therapeutics.

3.3. Chemical modifications and drug optimization

Given the inherent limitations associated with natural alkaloids, including toxicity and poor pharmacokinetic properties, chemical modification strategies have been widely explored to improve their therapeutic potential. Semi-synthetic derivatives and analog development have emerged as key approaches to enhance efficacy while reducing adverse effects.³⁴

For instance, modifications aimed at improving solubility and bioavailability have been applied to camptothecin derivatives, resulting in clinically approved drugs with improved pharmacological profiles.³⁵ Similarly, structural optimization of berberine and lycorine analogs has demonstrated enhanced anticancer activity and improved selectivity in experimental models.³⁶ In addition, advances in computational chemistry and molecular modeling have facilitated the rational design of alkaloid derivatives with improved target specificity. These approaches enable the identification of key binding interactions and support the development of compounds with optimized pharmacodynamic properties.³⁷

3.4. Implications for drug development

The link between chemical structure and biological activity underscores the necessity of combining phytochemistry with pharmacological assessment in anticancer drug research. Recognizing structural factors that influence activity aids in identifying promising compounds and facilitates the rational design of more effective, safer therapeutic agents, advancing the development of targeted cancer treatments.³⁸

Moreover, the complexity of alkaloid structures, while presenting synthetic challenges, also provides opportunities for the development of novel scaffolds with unique mechanisms of action. This diversity may be particularly valuable in addressing unmet needs in oncology, such as

drug resistance and tumor heterogeneity.³⁹

Taken together, these findings reinforce the concept that plant-derived alkaloids should be viewed not merely as isolated bioactive compounds, but as versatile chemical frameworks that can guide the development of next-generation anticancer therapies.⁴⁰

4. Anticancer activity across different cancer types

4.1. Breast cancer

Breast cancer is among the most frequently investigated malignancies in studies evaluating plant-derived alkaloids, reflecting both its global burden and the availability of well-established *in vitro* models. Across the reviewed literature, multiple alkaloids exhibited pronounced antiproliferative effects in breast cancer cell lines, including MCF-7 and other hormone-responsive and aggressive phenotypes. Highly potent compounds such as conofolidine demonstrated submicromolar activity, while classic alkaloids such as vincristine retained strong cytotoxicity through microtubule disruption and mitotic arrest.^{41,42}

In addition to direct cytotoxicity, several alkaloids showed mechanistic versatility in breast cancer models. Berberine and related compounds modulated apoptosis-related proteins, suppressed survival signaling, and altered oxidative stress responses, whereas jerantinine derivatives combined tubulin inhibition with polo-like kinase interference and reactive oxygen species generation.^{43,44} These observations suggest that breast cancer cells may be particularly susceptible to alkaloids capable of simultaneously targeting cell division and stress-adaptive pathways.

However, the evidence remains largely preclinical, and important differences exist among molecular subtypes. Estrogen receptor-positive, HER2-positive, and triple-negative models may respond differently to alkaloid exposure, highlighting the need for more subtype-specific investigation. This is particularly relevant because compounds with strong activity in one breast cancer context may display reduced efficacy or altered cell-death phenotypes in another.⁴⁵

4.2. Lung cancer

Lung cancer also represents a major focus of alkaloid-based anticancer research, particularly in non-small cell lung cancer models. Several studies reported significant growth inhibition, apoptosis induction, and suppression of invasion in lung cancer cells exposed to plant-derived alkaloids. Chelerythrine chloride, 11-methoxytabersonine, and related compounds demonstrated marked effects on

cell viability and colony formation, while also modulating pathways associated with stemness, migration, and epithelial–mesenchymal transition.^{46,47}

Microtubule-active alkaloids remain relevant in this setting, but the reviewed evidence also underscores the importance of signaling modulation in lung cancer. Alkaloids capable of affecting EGFR, Akt, STAT, and oxidative stress pathways may be especially valuable in tumors characterized by high signaling plasticity and acquired resistance to targeted therapies.⁴⁸ In this regard, some alkaloids exhibited not only cytotoxic effects but also chemosensitizing properties, which may enhance their translational relevance.

Another important observation is that anti-angiogenic and anti-metastatic activities appear particularly relevant in lung cancer models. Compounds such as solanidine and other structurally distinct alkaloids have been shown to interfere with hypoxia-driven signaling and vascular mediators, suggesting that their value may extend beyond simple tumor-cell killing to modulation of the tumor microenvironment.⁴⁹ This broader pharmacological spectrum may be advantageous in highly aggressive thoracic malignancies.

4.3. Colorectal cancer

Colorectal cancer emerged as one of the most extensively represented tumor types in the reviewed evidence, both *in vitro* and *in vivo*. This prominence is particularly important from a translational perspective because colorectal cancer models have been used not only for cytotoxicity screening but also for xenograft validation, anti-angiogenic assessment, and evaluation of drug combinations. Veratridine, for example, demonstrated significant tumor reduction in colorectal xenograft systems, supporting the relevance of alkaloid activity beyond cell-based assays.⁵⁰

In vitro, several alkaloids displayed strong growth inhibition in colorectal cancer cells through diverse mechanisms, including cell cycle arrest, oxidative stress induction, apoptosis, and modulation of DNA damage pathways. Some compounds also performed favorably when compared with standard agents such as 5-fluorouracil or etoposide, suggesting that at least a subset of alkaloids may have meaningful comparative potency in this tumor type.^{51,52}

Colorectal cancer is also a useful context for evaluating resistance-related phenomena. Because this malignancy often develops multidrug resistance and survival pathway redundancy, studies showing that specific alkaloids retain activity in resistant models are particularly valuable. The evidence indicates that some compounds can evade efflux transporters or interfere with resistance-associated

signaling, thereby preserving efficacy under otherwise unfavorable conditions.⁵³ This characteristic strengthens the rationale for further investigating alkaloids in colorectal oncology, especially in combination-based strategies.

4.4. Hematological malignancies

Hematological malignancies, including leukemia and lymphoma, appear especially sensitive to certain plant-derived alkaloids. Several compounds demonstrated low micromolar or submicromolar activity in leukemia cell lines, suggesting that these tumors may be particularly vulnerable to alkaloids affecting protein synthesis, apoptosis, or microtubule integrity.⁵⁴ Lycorine and related Amaryllidaceae alkaloids were notable in this regard, with strong activity reported in myeloid and lymphoid models.

This increased sensitivity may reflect both biological and pharmacological factors. Hematological cancers often exhibit high proliferative rates and dependence on tightly regulated cell-cycle and apoptotic mechanisms, which may render them more susceptible to multitarget compounds. In addition, drug access to circulating tumor cells differs fundamentally from that in solid tumors, potentially favoring the activity of compounds with otherwise suboptimal tissue penetration.⁵⁵

Nevertheless, despite the promising potency observed in hematologic models, the same translational barriers remain relevant. Toxicity, therapeutic window, and formulation constraints continue to limit development. Thus, although hematological cancers may represent one of the most promising indications for alkaloid-based therapies, advancement will still depend on improved pharmacological optimization and more robust *in vivo* validation.⁵⁶

4.5. Brain tumors and glioblastoma

Brain tumors, particularly glioblastoma, represent a challenging but highly relevant target for alkaloid research. The reviewed evidence indicates that selected alkaloids, including narciclasine and certain Amaryllidaceae-derived compounds, display meaningful activity in glioblastoma models through mechanisms involving suppression of proliferation, induction of cell death, and interference with tumor-supportive signaling pathways.⁵⁷

This is of particular interest because glioblastoma is characterized by extreme heterogeneity, therapeutic resistance, and poor prognosis. Multitarget alkaloids may offer advantages in such a context, especially when they combine antiproliferative activity with anti-invasive or anti-angiogenic effects. However, the treatment of brain tumors introduces an additional translational barrier: blood–brain barrier penetration. As a result, promising

in vitro activity alone is insufficient to support clinical relevance unless accompanied by formulation strategies or pharmacokinetic evidence suggesting adequate central nervous system exposure.⁵⁸

Accordingly, future work in this area should prioritize not only mechanistic efficacy but also delivery technologies capable of enhancing intracranial availability. This makes glioblastoma a compelling example of why pharmacology and formulation must be considered together in alkaloid development.

4.6. Ovarian, pancreatic, hepatic, and other solid tumors

Beyond the major cancer categories already discussed, plant-derived alkaloids also demonstrated activity across a broad spectrum of solid tumors, including ovarian, pancreatic, hepatic, gastric, bladder, and cervical cancers. In ovarian cancer models, some alkaloids were able to enhance cisplatin sensitivity and suppress prosurvival signaling, suggesting a possible role in overcoming chemoresistance.⁵⁹ In pancreatic cancer, camptothecin derivatives and related compounds displayed both direct cytotoxicity and favorable performance in organoid or xenograft-based systems, reinforcing their translational relevance.

In hepatic and gastric cancer models, alkaloids exhibited diverse effects ranging from apoptosis induction to inhibition of migration, invasion, and angiogenesis. This broad activity profile indicates that alkaloid pharmacology is not restricted to a narrow set of tumor types but instead spans multiple malignancies with distinct biological features.⁶⁰ At the same time, such breadth also emphasizes the importance of contextual interpretation: the same compound may induce apoptosis in one tumor type, senescence in another, and only modest cytostasis in a third.

Taken together, these data support the view that plant-derived alkaloids should not be considered as universally interchangeable anticancer agents. Rather, their development should be guided by tumor-specific biology, pharmacological context, and mechanistic fit. A more stratified approach may improve the likelihood of identifying clinically viable candidates.

The broad anticancer spectrum of plant-derived alkaloids reinforces their value as mechanistically rich lead compounds rather than merely empirical cytotoxins. However, the diversity of responses observed across tumor types also underscores a central challenge: strong experimental efficacy does not necessarily translate into favorable therapeutic performance. For this reason, a more detailed analysis of pharmacokinetics, toxicity, and

druggability is essential to understand why many alkaloids remain confined to the preclinical stage.

5. Pharmacokinetics and toxicological profile

5.1. Pharmacokinetic limitations of plant-derived alkaloids

Despite their demonstrated anticancer activity in experimental models, many plant-derived alkaloids present pharmacokinetic limitations that restrict their clinical applicability. Poor aqueous solubility, low oral bioavailability, rapid metabolic degradation, and inefficient systemic distribution collectively reduce effective drug exposure *in vivo*, contributing to the well-documented discrepancy between experimental efficacy and clinical performance,⁶¹ as illustrated in the translational pipeline presented in Figure 3.

A key factor underlying these limitations is extensive first-pass metabolism, which significantly decreases systemic availability. For instance, berberine exhibits limited oral bioavailability due to rapid hepatic metabolism and active efflux mediated by transport proteins such as P-glycoprotein.⁶² As a result, higher doses are often required to achieve therapeutic concentrations, potentially increasing the risk of toxicity.

In addition, the physicochemical properties of alkaloids, including lipophilicity and structural complexity, may impair tissue penetration and limit drug accumulation at target sites. This is particularly relevant for tumors located in pharmacologically protected environments, such as the central nervous system, where physiological barriers restrict drug access.⁶³

Furthermore, substantial variability in pharmacokinetic profiles among different alkaloid classes complicates the prediction of *in vivo* behavior. Even structurally related compounds may exhibit distinct absorption, distribution, metabolism, and excretion (ADME) characteristics, emphasizing the need for compound-specific evaluation.⁶⁴ The major limitations associated with alkaloid-based therapies and their potential solutions are summarized in Table 1.

5.2. Toxicological profile and selectivity

Toxicity remains one of the most critical challenges in the development of alkaloid-based anticancer therapies. While many alkaloids demonstrate potent cytotoxic effects against cancer cells, their selectivity toward malignant cells over normal tissues is often limited.⁶⁵

This lack of selectivity is particularly evident in compounds that target fundamental cellular processes,

Translational Pipeline of Plant-Derived Alkaloids in Anticancer Drug Development

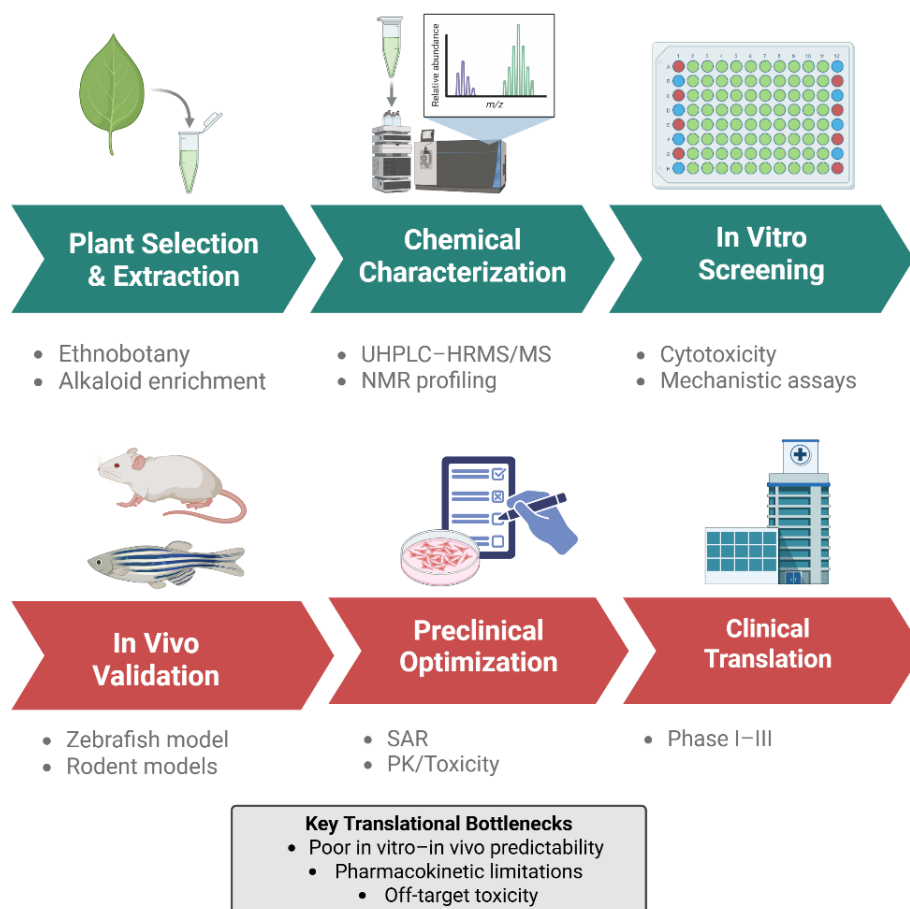


Figure 3. Translational pipeline of plant-derived alkaloids in anticancer drug development. The process includes plant selection, chemical characterization, *in vitro* screening, *in vivo* validation, preclinical optimization, and clinical translation. Key translational bottlenecks include poor *in vitro*–*in vivo* predictability, pharmacokinetic limitations, and off-target toxicity. Schematic created by the authors using BioRender.com. Jhuly, M. (2026) <https://BioRender.com/e7wq4ra>

Table 1. Major limitations of alkaloid-based anticancer therapies and proposed strategies.

Limitation	Description	Impact	Proposed strategy	Ref.
Low bioavailability	Poor aqueous solubility	Reduced therapeutic efficacy	Nanocarrier systems	61,97
Toxicity	Off-target interactions	Safety limitations	Structural optimization	43
Drug resistance	Efflux pumps (P-gp)	Reduced response	Combination therapy	18,77
Metabolic instability	Rapid biotransformation	Short half-life	Prodrug design	61
Tumor heterogeneity	Variable tumor biology	Therapeutic failure	Multi-target agents	2,32

such as microtubule dynamics or protein synthesis. Although these mechanisms are effective in suppressing tumor growth, they can also affect rapidly dividing normal cells, leading to adverse effects such as myelosuppression, gastrointestinal toxicity, and neurotoxicity.⁶⁶

In preclinical studies, several alkaloids have demonstrated dose-dependent toxicity, with therapeutic effects observed within a narrow concentration range. This narrow therapeutic window represents a significant barrier to clinical translation, as small variations in dosing may result in substantial toxicity.⁶⁷

Moreover, long-term toxicity and off-target effects remain insufficiently characterized for many plant-derived alkaloids. The absence of standardized toxicity assessment protocols further complicates the evaluation of safety profiles across different studies.⁶⁸

5.3. Strategies to improve pharmacokinetics and safety

To address the limitations associated with pharmacokinetics and toxicity, several strategies have been explored to enhance the therapeutic potential of plant-derived alkaloids. One of the most promising approaches involves the use of advanced drug delivery systems, including nanoparticles, liposomes, and polymer-based carriers.⁶⁹

These delivery systems can improve solubility, enhance bioavailability, and enable targeted delivery to tumor tissues, thereby reducing systemic exposure and minimizing adverse effects. For example, nanoparticle-based formulations of camptothecin derivatives have demonstrated improved stability and increased tumor accumulation in preclinical models.⁷⁰

Chemical modification represents another important strategy for optimizing pharmacological properties. Semi-synthetic derivatives of natural alkaloids have been developed to improve solubility, metabolic stability, and target specificity, resulting in compounds with more favorable pharmacokinetic and safety profiles.⁷¹

In addition, combination therapies may offer a means of reducing toxicity by allowing lower doses of individual agents while maintaining therapeutic efficacy. Alkaloids used in combination with conventional chemotherapeutics or targeted therapies may exhibit synergistic effects, thereby enhancing overall treatment outcomes.⁷²

5.4. Translational implications of pharmacokinetic and toxicological constraints

The pharmacokinetic and toxicological characteristics of plant-derived alkaloids play a decisive role in determining their translational success. While many compounds

demonstrate strong anticancer activity in preclinical models, unfavorable pharmacological properties often prevent their progression to clinical development.⁷³

This discrepancy highlights the importance of integrating pharmacokinetic and toxicity assessment early in the drug discovery process. Approaches that combine *in vitro* screening with predictive *in vivo* models, such as zebrafish systems, may provide a more accurate evaluation of therapeutic potential.⁷⁴

Furthermore, a shift toward a more holistic understanding of drug behavior—encompassing not only efficacy but also safety, metabolism, and delivery—is essential for improving the success rate of alkaloid-based therapies.⁷⁵

Taken together, these findings reinforce the notion that the primary limitation of plant-derived alkaloids in oncology is not their biological activity, but rather the challenges associated with optimizing their pharmacological profiles for clinical use.⁷⁶

6. Drug resistance and combination strategies

6.1. Mechanisms of drug resistance in cancer

Drug resistance remains one of the most significant challenges in cancer therapy and a major contributor to treatment failure. Tumor cells can develop resistance through multiple mechanisms, including increased drug efflux, enhanced DNA repair capacity, activation of survival signaling pathways, and evasion of apoptosis.⁷⁷

Among these mechanisms, overexpression of ATP-binding cassette (ABC) transporters, such as P-glycoprotein, plays a central role by actively exporting chemotherapeutic agents out of cancer cells, thereby reducing intracellular drug accumulation.⁷⁸ In addition, alterations in drug targets, epigenetic modifications, and metabolic reprogramming further contribute to resistance development.⁷⁹

The complexity of these resistance mechanisms underscores the need for therapeutic agents capable of targeting multiple pathways simultaneously. In this context, plant-derived alkaloids, with their multitarget pharmacological properties, represent promising candidates for overcoming drug resistance.⁸⁰

6.2. Alkaloids as modulators of drug resistance

Emerging evidence indicates that plant-derived alkaloids can modulate key pathways associated with drug resistance. Several compounds have been shown to inhibit efflux transporters, thereby increasing intracellular drug

concentrations and restoring sensitivity to conventional chemotherapeutic agents.⁸¹

In addition, alkaloids can interfere with survival signaling pathways such as PI3K/Akt/mTOR and NF- κ B, which are frequently upregulated in resistant tumors. By suppressing these pathways, alkaloids may sensitize cancer cells to apoptosis and enhance therapeutic response.⁸²

Some alkaloids also exhibit the ability to modulate the tumor microenvironment, including the inhibition of angiogenesis and suppression of inflammatory signaling, which can contribute to resistance.⁸³ These multifunctional effects highlight their potential as adjuvant agents in cancer therapy.

6.3. Combination therapies involving alkaloids

Combination therapy has emerged as a key strategy to overcome drug resistance and improve treatment outcomes in oncology. The use of plant-derived alkaloids in combination with conventional chemotherapeutic agents has shown promising results in preclinical studies.⁸⁴

Alkaloids may act synergistically with standard drugs by targeting complementary pathways. For example, combining microtubule-targeting alkaloids with DNA-damaging agents can enhance cytotoxic effects through simultaneous disruption of cell division and induction of DNA damage.⁸⁵

In addition, some alkaloids have demonstrated the ability to reverse resistance to commonly used drugs such as cisplatin and doxorubicin. This effect is often mediated by inhibition of efflux pumps, modulation of apoptotic pathways, or interference with cellular stress responses.⁸⁶

Another advantage of combination therapy is the potential to reduce the required dose of individual agents, thereby minimizing toxicity while maintaining or enhancing efficacy.⁸⁷

6.4. Challenges and limitations of combination strategies

Despite the potential benefits, combination therapies involving alkaloids also present several challenges. Drug-drug interactions, increased toxicity, and variability in pharmacokinetics can complicate treatment regimens and limit clinical applicability.⁸⁸

Furthermore, the optimal dosing, scheduling, and selection of combination partners remain poorly defined for many alkaloid-based therapies. The lack of standardized experimental protocols further complicates the interpretation of preclinical findings.⁸⁹

Another important limitation is the scarcity of clinical

data supporting the efficacy of alkaloid-based combination therapies. Most available evidence is derived from *in vitro* or animal studies, highlighting the need for well-designed clinical trials.⁹⁰

6.5. Translational implications and future perspectives

The ability of plant-derived alkaloids to modulate multiple resistance mechanisms represents a significant advantage in the development of anticancer therapies. Their incorporation into combination strategies may enhance therapeutic efficacy and overcome limitations associated with monotherapy.⁹¹

However, successful translation will require a deeper understanding of the molecular interactions between alkaloids and conventional drugs, as well as the development of optimized delivery systems to ensure adequate bioavailability and target specificity.⁹²

Future research should focus on integrating mechanistic insights with translational approaches, including advanced *in vivo* models and clinical validation. Such strategies may enable the rational design of combination therapies that maximize efficacy while minimizing toxicity.⁹³

7. Drug delivery systems and nanotechnology in alkaloid-based cancer therapy

7.1. Limitations of conventional drug delivery

One of the major barriers to the clinical application of plant-derived alkaloids is the inefficiency of conventional drug delivery systems. Many alkaloids exhibit poor solubility, instability under physiological conditions, and rapid systemic clearance, which significantly reduce their therapeutic efficacy.⁹⁴

In addition, nonspecific distribution of these compounds can lead to off-target effects and systemic toxicity, particularly in tissues with high proliferative rates. This limitation is especially relevant for alkaloids that target fundamental cellular processes, such as microtubule dynamics or protein synthesis.⁹⁵

Furthermore, biological barriers such as the blood-brain barrier and tumor microenvironment heterogeneity can restrict drug penetration and reduce effective concentrations at tumor sites.⁹⁶ These challenges underscore the need for more advanced and targeted delivery strategies.

7.2. Nanotechnology-based drug delivery systems

The application of nanotechnology in alkaloid-based therapy represents a strategic shift from conventional delivery approaches toward pharmacokinetic optimization.

Rather than merely improving solubility, nanocarrier systems redefine drug distribution, enabling controlled release, enhanced tumor accumulation, and reduced systemic exposure.⁹⁷ Emerging strategies to enhance the therapeutic efficacy of alkaloids are summarized in Table 2.

These systems enable controlled drug release and can enhance tumor targeting through passive mechanisms such as the enhanced permeability and retention (EPR) effect. As a result, higher concentrations of the drug can be delivered to tumor tissues while minimizing systemic exposure.⁹⁸

For example, nanoparticle formulations of camptothecin derivatives have demonstrated improved pharmacokinetic profiles and enhanced antitumor activity in preclinical models. Similarly, liposomal delivery systems have been shown to reduce toxicity and increase therapeutic efficacy for several alkaloids.⁹⁹

7.3. Targeted delivery and functionalization strategies

Beyond passive targeting, advanced nanocarrier systems can be functionalized with ligands that recognize tumor-specific receptors, enabling active targeting of cancer cells. This approach enhances drug accumulation at the tumor site and improves selectivity.¹⁰⁰

Functionalization strategies may include the use of antibodies, peptides, or small molecules that bind to overexpressed receptors on cancer cells, such as folate receptors or growth factor receptors. This targeted delivery not only increases therapeutic efficacy but also reduces damage to normal tissues.¹⁰¹

In addition, stimuli-responsive nanocarriers have been developed to release drugs in response to specific tumor microenvironment conditions, such as pH changes,

enzymatic activity, or redox gradients. These systems provide an additional level of control over drug release and may further improve therapeutic outcomes.¹⁰²

7.4. Integration with alkaloid pharmacology

The integration of nanotechnology with alkaloid pharmacology represents a significant advancement in anticancer drug development. By combining the potent biological activity of alkaloids with advanced delivery systems, it is possible to overcome many of the limitations that have historically hindered their clinical translation.¹⁰³

Nanocarriers can enhance the pharmacokinetic properties of alkaloids, improve their stability, and enable targeted delivery to tumor tissues. This approach may be particularly beneficial for compounds with narrow therapeutic windows, as it allows for more precise control of drug exposure.¹⁰⁴

Moreover, nanotechnology facilitates the co-delivery of multiple agents, enabling combination therapies within a single delivery system. This strategy may enhance synergistic effects and contribute to overcoming drug resistance.¹⁰⁵

7.5. Challenges and future perspectives

Despite the promising potential of nanotechnology-based delivery systems, several challenges remain. Issues related to large-scale production, reproducibility, regulatory approval, and long-term safety must be addressed before these systems can be widely adopted in clinical practice.¹⁰⁶

In addition, variability in tumor biology and patient-specific factors can influence the effectiveness of nanocarrier systems, highlighting the need for personalized approaches to drug delivery.¹⁰⁷ Future research should focus on optimizing nanocarrier design, improving targeting efficiency, and integrating delivery systems with advanced

Table 2. Emerging strategies to enhance the anticancer efficacy of alkaloids

Strategy	Description	Advantage	Example	Ref.
Nanoparticles	Drug encapsulation systems	Improved bioavailability	Liposomes	97
Combination therapy	Drug synergism	Overcomes resistance	Cisplatin combinations	45,50
SAR optimization	Structural modification	Improved potency	Lycorine derivatives	30
Metabolomics-guided therapy	Pathway-based targeting	Precision treatment	Aloperine	53

Abbreviation: SAR: Structure–activity relationship.

preclinical models, such as zebrafish and patient-derived xenografts. These efforts may enhance the predictive value of preclinical studies and accelerate the translation of alkaloid-based therapies into clinical applications.¹⁰⁸

8. Conclusion

Plant-derived alkaloids represent a mechanistically diverse class of compounds with consistent anticancer activity across experimental models. However, their limited clinical translation reflects not a lack of biological efficacy, but persistent challenges related to pharmacokinetics, toxicity, and methodological heterogeneity. The current evidence base remains heavily dependent on *in vitro* studies, often lacking standardization and robust *in vivo* validation, which weakens its predictive value for clinical application. In this context, the apparent potency of alkaloids should be interpreted with caution, as experimental conditions frequently overestimate therapeutic relevance. Future progress in this field will depend on the integration of mechanistic pharmacology with translational strategies, including standardized experimental frameworks, improved *in vivo* models, and advanced drug delivery systems.

Within this perspective, Amaryllidaceae alkaloids should be considered not as immediate drug candidates, but as valuable molecular scaffolds for rational drug design. Bridging the gap between experimental efficacy and clinical applicability remains the central challenge—and the key opportunity—for the development of alkaloid-based anticancer therapies.

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