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The Anti-Tumor Effects and Mechanisms of Harmine: From Molecular Actions to Translational Challenges

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Abstract

Harmine, a naturally occurring β-carboline alkaloid isolated primarily from *Peganum harmala*, has emerged as a promising anticancer compound based on extensive preclinical evidence. Studies demonstrate that harmine exerts antitumor effects across multiple malignancies, including breast, lung, colorectal, gastric, pancreatic, ovarian, and brain cancers. These effects are mediated through the modulation of diverse cellular and molecular mechanisms, such as inhibition of cell proliferation, induction of apoptosis and autophagy, suppression of epithelial–mesenchymal transition, inhibition of angiogenesis, and regulation of oncogenic signaling pathways including PI3K/AKT, p53, and Hippo signaling. Recent findings further suggest that harmine may influence components of the tumor microenvironment, thereby extending its antitumor activity beyond direct cancer cell targeting. Despite these encouraging results, clinical translation of harmine remains limited due to challenges including central nervous system toxicity, poor solubility, and insufficient pharmacokinetic characterization. This review critically evaluates the current evidence on the antitumor mechanisms of harmine, highlights key translational barriers, and discusses future strategies to facilitate its development toward clinical oncology. **Keywords:** Harmine, β-carboline alkaloids, Oncology, Anticancer mechanisms, Natural products.

Introduction

Natural products continue to represent a cornerstone of anticancer, antibacterial, anti-inflammatory, antifungal, antioxidant, anti-diarrheal, anti-ulcer, gastroprotective, and anti-constipation effects in drug discovery, functioning either as therapeutic agents or as lead scaffolds for further chemical optimization [1-7]. Despite remarkable advances in targeted therapies and immunotherapies, a substantial proportion of drugs currently used in clinical oncology originate from natural sources, highlighting their enduring relevance in cancer treatment [8]. β-Carboline alkaloids have attracted considerable attention due to their diverse biological activities, including anti-inflammatory, neuroactive, and anticancer properties [9]. Among these compounds, harmine, primarily isolated from *Peganum harmala,* is the most extensively investigated. Early studies focused mainly on its effects on the central nervous system, particularly its role as a monoamine oxidase inhibitor. However, subsequent investigations demonstrated that harmine also exhibits significant cytotoxic and antiproliferative effects against cancer cells [10,11]. Over the past two decades, accumulating preclinical evidence has shown that harmine suppresses tumor growth across a broad spectrum of malignancies, including lung, breast, colorectal, gastric, pancreatic, ovarian, and brain cancers [12]. Unlike many natural compounds, harmine exerts its anticancer effects through the modulation of multiple cellular and molecular processes. These include inhibition of cell proliferation, induction of apoptosis, suppression of epithelial–mesenchymal transition, inhibition of angiogenesis, and regulation of key oncogenic signaling pathways such as PI3K/AKT, p53, and Hippo signaling [13,14]. Recent studies have further suggested that harmine may influence components of the tumor microenvironment, including endothelial and immune cells, thereby extending its antitumor activity beyond direct interactions with cancer cells [15].

Despite these promising preclinical findings, harmine has not yet advanced to clinical application. Central nervous system toxicity, limited solubility, and insufficient pharmacokinetic characterization remain major barriers to its translational development [9]. Although several reviews have summarized the anticancer properties of harmine, many adopt a predominantly

descriptive approach and provide limited critical evaluation of experimental robustness or translational relevance [16]. Therefore, this review aims to critically assess the current evidence regarding the anticancer mechanisms of harmine, identify key translational challenges, and highlight future research priorities necessary to facilitate its progression toward clinical oncology.

Material and Methods

This article employs a narrative literature review methodology to examine the anti-tumor effects and molecular mechanisms of harmine, with particular emphasis on translational challenges. A comprehensive search of the scientific literature was conducted using international databases, including PubMed, ScienceDirect, ProQuest, ResearchGate, and Google Scholar, to retrieve relevant secondary data. The search focused on studies investigating the anticancer properties of harmine, its underlying molecular mechanisms, and barriers to clinical translation. Eligible publications included original research articles and review papers published between 2010 and 2025. Studies were selected based on their relevance to harmine-mediated anticancer activity, mechanistic insights, and translational significance.

Discussion

The collected evidence reviewed in this article highlights harmine as a pharmacologically versatile β-carboline alkaloid whose antitumor activity arises from both its chemical scaffold and its ability to influence multiple cancer-associated pathways. Structural–activity relationship studies consistently demonstrate that harmine's planar heteroaromatic framework enables interactions with diverse intracellular targets, which likely explains its broad anticancer activity but also contributes to off-target effects, particularly within the central nervous system [17]. Chemical modifications at specific positions on the harmine scaffold, most notably C2, C7, and N9, have therefore been pursued as a strategy to enhance therapeutic selectivity while mitigating toxicity. Among these, C2 substitution—especially N2-benzylation—has shown the most consistent enhancement of cytotoxic potency across multiple cancer models and in vivo xenografts, often through increased reactive oxygen species generation and suppression of PI3K/AKT signaling [18].

However, the reliance on oxidative stress as a cytotoxic mechanism raises concerns regarding damage to normal tissues and reinforces the need for careful dose optimization and safety assessment.

Modifications at the C7 position appear to offer a more favorable balance between efficacy and tolerability. Replacement of the native methoxy group with bulkier substituents has been associated with reduced neurotoxicity while largely preserving anticancer activity, potentially through altered blood–brain barrier penetration or reduced neuronal target engagement [19].

In contrast, alterations at the N9 position have yielded inconsistent outcomes, with some derivatives demonstrating increased potency at the cost of a narrower therapeutic field [20]. These findings collectively suggest that a rational combination of structural modifications, rather than single-site optimization, may be required to achieve clinically meaningful improvements in harmine-based compounds.

At the cellular level, harmine exerts direct antitumor effects through inhibition of proliferation, disruption of cell-cycle progression, and induction of programmed cell death across a wide range of malignancies [21]. Importantly, these effects are not uniform across tumor types. Some studies report G0/G1 arrest associated with downregulation of cyclins and upregulation of cyclindependent kinase inhibitors, while others identify G2/M arrest mediated by suppression of AKT and mTOR signaling, particularly in pancreatic cancer and glioblastoma models [22]. The observation that certain harmine analogues can inhibit proliferation independently of p53 status is especially noteworthy, given the high prevalence of p53 dysfunction in clinical tumors [23]. These context-dependent effects highlight the importance of tumor genotype and signaling dependency in determining therapeutic response.

Apoptosis induction represents another major mechanism underlying harmine's anticancer activity. Across multiple cancer models, harmine activates intrinsic apoptotic pathways through modulation of the Bax/Bcl-2 ratio, mitochondrial membrane destabilization, and caspase activation, often accompanied by elevated reactive oxygen species [24]. Evidence from related β-carbolines, such as harmaline, further suggests that death receptor–mediated extrinsic pathways may also contribute to tumor cell elimination [25]. Nevertheless, many studies rely heavily on molecular markers rather

than comprehensive functional assays, and the relatively high concentrations required to induce apoptosis in vitro raise legitimate questions regarding selectivity and clinical feasibility.

Beyond effects on tumor cell survival, harmine has demonstrated the capacity to suppress migration, invasion, and epithelial–mesenchymal transition, processes that are critical for metastatic progression. In breast cancer and glioblastoma models, harmine modulates key transcriptional regulators such as TAZ and Twist1, leading to reduced expression of mesenchymal markers and matrix metalloproteinases [26]. These findings suggest that harmine may preferentially target invasive and therapy-resistant phenotypes, although most evidence is derived from two-dimensional assays, and validation in orthotopic or spontaneous metastasis models remains limited. An important expansion of harmine research involves its effects on the tumor microenvironment. Anti-angiogenic activity has been demonstrated through direct inhibition of endothelial cell proliferation, migration, and survival, with mechanistic links to disruption of p53–MDM2 interactions and subsequent p53 stabilization [27]. Additional studies report suppression of angiogenic signaling pathways, including VEGF-A and PI3K/AKT, although reliance on surrogate assays necessitates cautious interpretation [28]. Given the central role of p53 in normal vascular homeostasis, further investigation is required to determine whether these effects can be selectively exploited in tumors without compromising physiological angiogenesis.

Emerging evidence also suggests that harmine may influence antitumor immunity. Enhancement of antigen presentation machinery and increased infiltration of cytotoxic immune cells have been observed in melanoma models, resulting in improved responses to immune checkpoint blockade. Identification of DYRK1A inhibition as a potential mechanism positions harmine as an immunesensitizing agent rather than a classical immunotherapeutic. However, these findings are currently restricted to a limited range of immunogenic tumor models, and broader applicability remains uncertain [29].

Combination therapy studies further support harmine’s translational potential. Harmine has been shown to enhance the efficacy of chemotherapeutic agents such as temozolomide, gemcitabine, and paclitaxel by suppressing resistance-associated signaling pathways and invasive behavior [30].

Despite encouraging synergy, most studies lack comprehensive pharmacokinetic and toxicity profiling, limiting extrapolation to clinical settings.

Finally, toxicity and pharmacological limitations remain major barriers to clinical translation. Neurotoxicity linked to central nervous system penetration and monoamine oxidase inhibition is consistently reported, while oxidative stress raises concerns regarding collateral tissue damage [31]. Although advances in targeted derivatives, localized delivery systems, and nanocarrier-based formulations have improved tumor selectivity and reduced adverse effects, comparative evaluation and long-term safety data are still insufficient [32].

In conclusion, the current literature positions harmine as a promising lead compound with multifaceted antitumor activity rather than a clinically mature anticancer drug. Future progress will depend on integrating structure-guided optimization with rigorous mechanistic validation, pharmacokinetic characterization, and safety assessment in clinically relevant models to determine whether harmine-based strategies can be realistically advanced toward oncology practice.

Conclusion

Harmine is a naturally occurring β-carboline alkaloid that has demonstrated broad antitumor activity across multiple cancer types in preclinical studies. Its anticancer effects are mediated through the regulation of diverse molecular pathways involved in cell proliferation, apoptosis, angiogenesis, and tumor progression, highlighting its multi-target therapeutic potential. However, the clinical translation of harmine remains limited due to challenges such as neurotoxicity, poor solubility, and insufficient pharmacokinetic evaluation. Future research should focus on optimizing harmine through chemical modification, advanced delivery systems, and combination strategies to improve its safety and translational feasibility. Addressing these challenges will be essential to determine whether harmine can advance from experimental research to clinical oncology.

Conflict of Interest

The authors declare no conflict of interest.

Declarations

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