



Harmine: A Natural β -Carboline with Promising Multi-Targeted Anticancer Potential

Noshin Tasnim Yana¹, Md. Nasimul Haque Shipon¹, Md Emran Hossain², Md. Sakib Al Hasan^{1*}, Md. Tahmidur Rahman¹, Emon Mia¹

Abstract

Cancer remains a major global health challenge, driving an urgent search for safer and more effective therapeutics from natural sources. Harmine (HRM), a β -carboline alkaloid found predominantly in *Peganum harmala* and *Banisteriopsis caapi*, has long been valued in traditional medicine for its diverse pharmacological properties. This study systematically reviewed preclinical and computational evidence to evaluate HRM's anticancer potential, safety, and pharmacological suitability. Data were collected from PubMed, ScienceDirect, Springer, and Web of Science databases up to February 2025, focusing on in vitro and in vivo studies of HRM's effects on various cancer types. Additionally, SwissADME and ProTox-II were used to assess drug-likeness and toxicity profiles. Results revealed that HRM inhibits cancer cell proliferation, migration, and invasion while inducing apoptosis, autophagy, and cell cycle arrest across a broad spectrum of cancers—including breast, colon, gastric, liver, lung, thyroid, and skin malignancies. Mechanistically, HRM activates caspase-3/-9 and PARP cleavage, upregulates pro-apoptotic proteins (Bax, p53), and downregulates oncogenic regulators (cyclin D1, p-Akt, and Bcl-2). In silico analyses indicated favorable physicochemical and

pharmacokinetic characteristics, with compliance to all major drug-likeness rules and moderate oral bioavailability. Toxicological predictions suggested manageable safety risks, though potential hepatotoxicity and MAO-A inhibition warrant cautious evaluation. In conclusion, harmine demonstrates potent, multi-targeted anticancer properties with strong preclinical evidence supporting its advancement as a natural therapeutic lead. Further pharmacokinetic optimization and clinical validation are essential to confirm its safety and efficacy in humans.

Keywords: Harmine, Anticancer activity, Apoptosis, Cytotoxicity, Natural product.

1. Introduction

Cancer, a disorder of cell proliferation, may lead to tumor production, and it is still an uncontrolled disease and a major cause of death worldwide (Islam and Dantas, 2013). As per the World Health Organization, in 2020, cancer was the sole reason for the death of more than 10 million individuals (Asif Ali et al., 2023). In 2030, the global cancer death toll is projected to rise by 75%, with middle and low-income countries being most affected (Bhuia et al., 2023a). By 2050, the total number of cancer cases is projected to increase to 35.3 million, an increase of 76.6% from the 2022 estimate of 20 million (Bizuyeyu et al., 2024). Currently, there are different methods for cancer treatment available based on cancer type and grade, such as radiation or chemotherapy, and other options like immunotherapy, targeted therapy, and hormone therapy employed in cancer patients. The chemotherapeutic approach is used for the

Significance | Harmine shows multi-targeted anticancer activity, offering potential as a natural, safer alternative to conventional chemotherapy for various cancers.

*Correspondence. Md. Sakib Al Hasan, Department of Pharmacy, Gopalganj Science and Technology University, Gopalganj 8100, Bangladesh
E-mail: mdsakibalhasan192412@gmail.com

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Author Affiliation.

¹ Department of Pharmacy, Gopalganj Science and Technology University, Gopalganj 8100, Bangladesh

² Department of Applied Nutrition and Food Technology, Kushtia-7003, Bangladesh.

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treatment of benign and malignant cancers; however, it has several limitations, like side effects and off-target effects (Elumalai et al., 2022). Increasing attention is being paid to the possibility of applying cancer chemopreventive agents for individuals at high risk of neoplastic development. For this purpose, natural compounds have practical advantages with regard to availability, suitability for oral application, regulatory approval, and mechanisms of action (Tsuda et al., 2004). Natural products have marked the history of anticancer drug discovery. A number of widely-used anticancer therapeutics originate from natural sources, such as irinotecan from *Camptotheca acuminata* (Huang et al., 2021; Kciuk et al., 2020), vincristine from *Catharanthus roseus* (Huang et al., 2021; Škubník et al., 2021), etoposide from *Podophyllum peltatum* (Huang et al., 2021; Kluska and Woźniak., 2021), and paclitaxel from *Taxus brevifolia* (Huang et al., 2021; Zhu and Chen., 2019).

Harmine (HRM) is isolated from the seeds of the medicinal plant, *P. harmala* L., which grows in arid areas, such as the Middle East and some provinces of China, and has been widely used in folk medicine for a long time. HRM has many pharmacological activities, including anti-inflammatory (Filali et al., 2015), neuroprotective (Kadyan and Singh, 2024), antidiabetic (Morsy et al., 2023), and antitumor activities (Zhang et al., 2020). HRM has demonstrated its ability to suppress cancer cells by coordinating multiple complex mechanisms. Its activation of Myt1, phosphorylation and deactivation of Cdk2, and overexpression of p21, which results in G2 phase cell cycle arrest, are examples of how it causes apoptosis and inhibits proliferation (Timbilla et al., 2024).

In this study, a comprehensive review was conducted to explore the anticancer potential of harmine, a natural compound found in *Peganum harmala*. Relevant scientific articles were collected from trusted online databases such as PubMed, ScienceDirect, Springer, and Wiley Online Library, covering publications up to February 28, 2024. The keyword "Harmine" was used along with more than 15 related terms including "cancer," "tumor," "cytotoxic activity," "pharmacological activities," and others to ensure a wide and relevant search. Among the collected studies, those involving preclinical experiments using animal models, tissues, or cell cultures were selected for further analysis. To assess the drug development potential of harmine, the study also used AI-based tools. Specifically, SwissADME was used to evaluate the compound's drug-likeness, and ProTox II was applied to predict its toxicity profile. These tools provided insights into the safety and usability of harmine as a future anticancer drug candidate (Chamberlain et al., 2017; Mvondo et al., 2021).

This review was necessary because although several studies have investigated harmine's anticancer properties, the mechanisms at the cellular and molecular level had not been thoroughly summarized in a structured way. There is also an urgent need for safe, affordable, and natural alternatives to conventional cancer therapies. Harmine

shows strong promise in this area, and by combining literature review with modern AI-based screening tools, this study aims to support future development of harmine-based anticancer therapies.

2. Materials and methods

2.1 Study Design

This study was designed as a systematic literature review to evaluate the anticancer potential of harmine, a natural compound from *Peganum harmala*. Relevant articles were collected from databases including PubMed, ScienceDirect, Springer, Wiley Online, Web of Science, and Google Scholar, using the keyword "Harmine" along with related terms such as "cancer," "tumor," "cytotoxicity," and "biological activity." Studies involving preclinical models (in vitro/in vivo), harmine dosage, cancer types, and mechanisms of action were selected. Additionally, SwissADME was used to assess drug-likeness, and ProTox II to predict toxicity, providing insights into harmine's potential as a safe and effective anticancer drug.

2.2 Literature Search strategy

The information was gathered up until February 28, 2025, by using the common keyword "Harmine" to search online databases like PubMed, Wiley Online, Springer Link, ScienceDirect, Web of Science, and Google Scholar. This was followed by the terms "cancer," "tumor," "anticancer activity," "antitumor activity," "antiproliferation activity," "human cancer," "cytotoxic activity," "biological activities," "pharmacological activities," "pharmacological effects," "chemical features," "biological sources," "in vivo studies," or "in vitro studies." There were no limitations on time or language in the search parameters. The sources, concentration/dose, testing procedure, suggested action mechanism, overall conclusion, and recommendations were all included in the detailed review of the investigations.

2.3 Inclusion criteria

The following were the evaluation's inclusion criteria: (1) research involving laboratory animals or tissue or cell cultures; (2) research on the medicinal qualities and plant origins of HRM; (3) research showing that HRM is a bioactive compound in preclinical studies of plant extracts; (4) research with or without suggested mechanisms of action; (5) research demonstrating that HRM has synergistic effects after combined with other compounds; (6) studies using HRM derived from natural sources; and (7) research investigating the biopharmaceutical properties of HRM.

2.4 Exclusion criteria

The following were the exclusion criteria: (1) redundant information, titles, or abstracts that did not fit the criteria for inclusion; (2) case studies, letters, editorials, or commentary; (3) publications that were not written in English; and (4) research papers that were not published or that were not finished.

2.5 Drug-Likeness Properties

The drug-likeness of harmine was evaluated using the SwissADME (<http://www.swissadme.ch/>) web tool developed by the Swiss Institute of Bioinformatics. The SMILES structure of harmine was entered into the tool to compute its physicochemical, lipophilicity, water solubility, pharmacokinetics, and drug-likeness parameters. Drug-likeness was predicted based on compliance with standard medicinal chemistry filters, including Lipinski's Rule of Five, Ghose, Veber, Egan, and Muegge rules. The bioavailability score and consensus LogP were also recorded to assess its oral absorption potential.

2.6 Toxic Prediction

The toxicity prediction of harmine was conducted using the ProTox-II web server (https://tox-new.charite.de/protox_II), a computational platform that utilizes machine learning algorithms trained on experimental toxicity data. The SMILES (Simplified Molecular Input Line Entry System) notation of harmine was entered into the system to assess multiple toxicity endpoints. These included LD₅₀ (median lethal dose), hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity, along with predicted interactions with toxicological targets such as cytochrome P450 enzymes and nuclear receptors. The tool assigns the compound to one of six toxicity classes, based on the globally harmonized system (GHS) for chemical classification.

3. Results and Discussion

3.1 Botanical sources of Harmine

Since ancient times, people have utilized plants as medicine. The usage and promotion of medicinal plants can improve contemporary preventative measures, and they are essential in the fight against disease. Furthermore, these plants natural chemicals provide a useful supply of medicinal biomolecules (Devi et al., 2021; Qadir and Raja, 2021). Many plant groups, including the Nitrariaceae, Malpighiaceae, and Passifloraceae, have yielded HRM, a vital physiologically active component (Javeed et al., 2018; Mayad et al., 2019; de Frias et al., 2012; Khan and Nabavi, 2019). Several plants, including *P. harmala*, *B. caapi*, *Passiflora incarnata*, *Tribulus terrestris*, and *Zygophyllum fabago*, are widely used medicinal herbs and significant sources of HRM (Moloudizargari et al., 2013; Callaway, 2005; Frye and Haustein, 2007; Nikam et al., 2009; Dana et al., 2010). Moreover, the botanical sources, plant portion of HRM are exhibited in Table 1.

3.2 Anticancer activity of Harmine: Based on cancer

3.2.1 Blood cancer

Blood cancer is a type of cancer that affects the production and function of blood cells, originating in the bone marrow or lymphatic system (Rahimi Darehbagh and Rezaei, 2024). Blood cancers account for approximately 7% of all cancer cases worldwide, with leukemia, lymphoma, and myeloma collectively causing over 1 million new cases annually (Aljamali et al., 2021).

Depending on the kind and stage, treatment options for blood cancer may include immunotherapy, targeted therapy, radiation therapy, chemotherapy, and stem cell transplantation (Sharma et al., 2025). In our study, Oodi et al. (2017) found that HRM (1.6–102.4 µg/mL) increased p15 and DNMT1 levels in NB4 blood cancer cells, leading to increased DNA methylation and cell proliferation (Oodi et al. 2017).

3.2.2 Breast cancer

Globally, breast cancer is increasingly being diagnosed as the most common cancer (Wilkinson and Gathani, 2022). The mortality rates from breast cancer have risen dramatically over the past 20 years, according to global epidemiological studies that have been published (Azamjah et al., 2019). Breast cancer is a complicated process that encompasses multiple cell types, making prevention challenging everywhere. Early detection is one of the best strategies to prevent breast cancer (Sun et al., 2017). Systemic therapy, locoregional therapy, radiation therapy, and surgery are all part of the multidisciplinary approach used to treat breast cancer. Among the several types of systemic therapy are hormone therapy for hormone-positive diseases, chemotherapy, anti-HER2 therapies for HER2-positive diseases, and, most recently, immunotherapy (Tong et al., 2018; Wang and Wu., 2023). According to our current study, HRM has demonstrated significant anticancer efficiency against brain cancer in both in vitro and in vivo investigations. In the MDA-MB-231 and MCF-7 cell lines (0 – 200 µM), it induces apoptosis by increasing the pro-apoptotic factor Bax and decreasing the anti-apoptotic factor Bcl-2, while decreasing cell proliferation and migration by inhibiting p-Erk and p-Akt (Ding et al., 2019). By using nude BALB/c mice, Ding et al. (2019) also showed that HRM (20–80 mg/kg) significantly inhibited tumour growth. A study by Atteya et al. (2017) reported that HRM (0.1–100 µM) produced cytotoxicity and inhibiting colony formation in MCF-7 cell lines (Atteya et al., 2017). According to the study of Ma et al. (2010), the treatment of MDA-MB-231 breast cancer cells with HRM (1–50 µM) induces cytotoxicity and fluorescence intensity while decreasing Breast cancer resistance protein (BCRP) dependent efflux and mitoxantrone (Ma et al., 2010). A study by Yao et al. (2023) investigated that HRM induces cytotoxicity, apoptosis, and PTEN expression while decreasing proliferation, migration, invasion, N-cadherin, and vimentin (Yao et al., 2023). HRM has a significant anticancer effect on MDA-MB-231 cells at 30 µg/mL, triggering apoptosis by upregulating Puma, Bax, Bid, TRAIL, Caspase-8, p53, and p21, while downregulating Bcl-2 and inhibiting cell proliferation (Hashemi Sheikh Shabani et al., 2015). The compound exhibits cytotoxic effects toward MDA-MB-231 and MCF-7 breast cancer cells, which increase apoptosis and fluorescence intensity while reducing DNA topoisomerase II activity, cell cycle progression, and proliferation (Tang et al., 2023). Zhao and Wink (2013), also showed that HRM induces cytotoxicity

Table 1. Botanical sources and plant parts containing harmine (HRM)

Plant name	Plant parts	References
Peganum harmala L.	Seeds, roots	Timbilla et al., 2024
		Patel et al., 2012
		Zhang et al., 2020
		Dos Santos and Hallak, 2017
		Kartal et al., 2003
		El Fissi et al., 2024
Banisteriopsis caapi	Stem, bark	Berrougui et al., 2006
		Brito-da-Costa et al., 2020
Passiflora incarnata L.	Fruits, Seeds	SRS Mota et al., 2020
		Frison et al., 2008

by increasing p53 and p21. Which also decreased cell proliferation, Telomerase activity, hTERT mRNA expression, CDK2, c-Myc and cell growth (Zhao and Wink, 2013).

3.2.3 Colon cancer

Colon cancer is one of the most common types of cancer in the world and a leading cause of death (Gandomani et al., 2017). Age, race, diet, and the presence of inflammatory bowel disease are warning signs for colon cancer. The incidence of colon cancer is often intermittent. Obesity, alcohol consumption, smoking, and inactivity have all been identified as risk factors for colon cancer (Carethers, 2018; Rasool et al., 2013). Chemotherapy, surgery, targeted therapy, radiation therapy, and immunotherapy are among the treatments for colon cancer (Shinji et al., 2022). HRM expressed a potent anti-cancer effect against several colon cancer cells in both in vitro and in vivo studies. In SW620 colon cancer cells (0-20.00 µg/ml) with an IC₅₀ value of 5.13 µg/ml, it induced cell cycle arrest, apoptosis, and cytotoxicity by upregulating Bax, caspase-3/-9, and cyclin A while downregulating Bcl-2, Mcl-1, p-ERK, and p-Akt (Liu et al., 2016). A study by Li et al. (2020) showed that HRM at 1-300 µg/mL induced apoptosis while decreasing proliferation, migration, invasion, and metastasis as well as VEGF, MMP 2, MMP 9, TGF-β, and the EMT pathway (Li et al., 2020). Additionally, an in vivo study by Li et al. (2020) using BALB/c male mice (n=3) and HRM (30 mg/kg (t.v.)) significantly suppressed the tumor growth (Li et al., 2020).

3.2.4 Gastric cancer

A malignant growth that grows in the lining of the stomach is called gastric cancer (Piazuelo and Correa, 2013). Due to risk factors like diet, smoking, and H. pylori infection, gastric cancer is one of the main causes of cancer-related deaths worldwide and is more common in East Asia, Eastern Europe, and South America (Rawla and Barsouk, 2019). In our study, HRM showed strong anti-cancer efficacy against gastric cancer in vitro and in vivo across several cell lines. In MGC-803 and SGC-7901 cells (10-80 µM), HRM triggers autophagy, apoptosis, and cytotoxicity by increasing Bax, cleaved-PARP, cleaved-caspase 3, and inhibiting the PI3K/Akt/mTOR pathway, AMPK, and Bcl-2 (Li et al., 2017). Zhang et al. (2014)

investigated that treatment of BGC-823 and SGC-7901 cells (0-16 µg/ml) with HRM produces apoptosis by increasing Bax and decreasing Bcl-2. It also inhibits cell proliferation, migration, invasion, COX-2, PCNA, and MMP-2 (Zhang et al., 2014). In SGC-7901 cells (1-16 µg/ml), the compound induced apoptosis and decreased cell proliferation by increasing Bax and inhibiting Bcl-2 (Yu et al., 2016). According to an in vitro study by Sun et al. (2015), in SGC-7901 and MKN-45 cells at 1-16 µg/ml induces apoptosis while decreasing cell proliferation, migration, invasion, MMP-9, and COX-2 expression (Sun et al., 2015). In vivo, treatment with 15-60 mg/kg (i.p.) in athymic nude mice significantly inhibits tumour growth, while 30 mg/kg (i.p.) effectively suppresses tumor growth in female athymic nude mice.

3.2.5 Glioma cancer

Glioma is a type of tumor that originates in the glial cells of the brain or spinal cord (Ohgaki and Kleihues, 2005). The World Health Organization divides gliomas, the most prevalent kind of primary brain tumor, into four different categories according to histological characteristics such as cellularity, nuclear anatomy, mitotic action, necrosis, and vascular development (Louis, 2016). Despite rigorous multimodality treatment with chemotherapy, external beam radiation therapy, and surgery, the most prevalent type, glioblastoma multiforme, a grade IV glioma, has a median survival of 14-15 months (Stupp et al., 2005). In our study, HRM (1-10 µM) inhibited cell proliferation and migration in U-87 MG cells with IC₅₀ by downregulating the MMP-3 and AKT pathways (Chin et al., 2021).

3.2.6 Liver cancer

One of the main causes of cancer-related deaths worldwide is liver cancer, which can be caused by a variety of factors, including non-alcoholic fatty liver, smoking, alcohol consumption, obesity, diabetes, iron overload, and B or C hepatitis virus infections (Chuang et al., 2009; (Tufael, 2024). Oncolytic viral therapy, immunotherapy, cytotoxic chemotherapy, and traditional frontline therapy are used to treat liver cancer (Jebar et al., 2015). In HepG2 and Hep3B liver cancer cells, HRM (0-8 µM) enhanced cell death, apoptosis, and PI3K/AKT/mTOR signaling while decreasing

Table 2. Summary of anticancer activities of harmine across various cancer types

Sources	Cancer type	Experimental model/ cell lines	Tested Concentrations, (R/A)	IC50	Mechanisms	References
Peganum harmala	Breast cancer	MDA-MB-231 and MCF-7 cell lines, in vitro	0-200 μ M	-	↑Apoptosis, Bax ↓Cell proliferation, migration, tumour growth, TAZ, p-Erk, p-Akt, Bcl-2, Xenograft growth	Ding et al., 2019
		Nude BALB/c mice, in vivo (n=5)	20-80 mg/kg (i.p.)			
Peganum harmala	Gastric cancer	MGC-803 and SGC-7901 cell lines, in vitro	10-80 μ M	7.50-58.84 μ M and 1.77-40.94 μ M	↑Autophagy, apoptosis, Bax, cleaved-PARP, cleaved-caspase 3, cytotoxicity, Beclin-1, LC3-II, p62, cell death ↓PI3K/Akt/mTOR, AMPK, Bcl-2	Li et al., 2017
Peganum harmala	Lung cancer	HepG2 and S180 cell lines, in vitro	40 μ g/ml	0.011- 0.021 μ mol/ml	↑Apoptosis, Fas, mitochondrial perturbation, neuronal activity, neurotoxicity ↓Tumour growth, Topoisomerase I and II, microtubule formation, Bcl-2	Chen et al., 2005
		C ₅₇ BL/6 mice, in vivo (n=8)	7.5 mg/kg (i.v.)			
-	Thyroid cancer	TPC-1 cell line, in vitro	2-64 μ g/mL	16.57 $\pm$ 1.4, 9.48 $\pm$ 1.1, and 5.51 $\pm$ 0.7 μ g/mL	↑Apoptosis, Bax, cytotoxicity, Caspase-3 ↓Proliferation, colony formation, migration, invasion, cell growth, Bcl-2	Ruan et al., 2017
		Male and Female nude mice, in vivo (n=6)	4, 8, 16 μ g/mL (i.v.)			
-	Breast cancer	MCF-7 cell line, in vitro	0.1-100 μ M	-	↑Cytotoxicity ↓Colony formation, DYRK1A	Atteya et al., 2017
-	Breast cancer	MDA-MB-231 cell line, in vitro	1-50 μ M	40.51 $\pm$ 16.12 μ M	↑Cytotoxicity, mitoxantrone retention, fluorescence intensity ↓BCRP dependent efflux, mitoxantrone efflux	Ma et al., 2010
-	Pancreatic cancer	PANC-1, CFPAC-1, SW-1990, and BxPC-3 cell lines, in vitro	0-40 μ M	5.40 μ M and 13.67 μ M	↑Apoptosis, p21, cyclin B1, cytotoxicity, caspase-3, trabecular bone mass ↓Colon formation, Proliferation, c-Myc, AKT, mTOR pathway	Wu et al., 2019
Peganum harmala L	Breast cancer	MDA-MB-231, SKBR3, MCF-7 and MCF-10A cell lines, in vitro	0-240 μ M		↑Cytotoxicity, apoptosis, PTEN expression, E-cadherin ↓Proliferation, migration, invasion, epithelial-mesenchymal transition, N-cadherin, vimentin, malignant phenotypes, proliferation, PI3K, p-AKT, p-mTOR	Yao et al., 2023
-	Ovarian cancer	SKOV-3 cell line, in vitro	0-30 μ M	-	↓Cell proliferation, migration, Basal phosphorylation level, EGF, VEGF, MMP-2, MMP-9, cell growth, colony formation, PCNA, ERK1/2 phosphorylation, CREB	Gao et al., 2017
Peganum harmala	Skin cancer	B16F-10 cell line, in vitro	0.5-2 μ g/m	-	↑Apoptosis, Bax, Caspase-3, Caspase-9, p53, Caspase-8, Bid, inflammation, tumour metastasis ↓Bcl-2, cell growth	Hamsa et al., 2011
-	Glioma cancer	U-87 MG cell line, in vitro	1-10 μ M	7.9 μ M	↓MMP-3, proliferation, migration, AKT	Chin et al., 2021
-	Liver cancer	HepG2 and Hep3B cell lines, in vitro	0-8 μ M	-	↑Cell death, colony formation, PI3K/AKT/mTOR, apoptosis ↓Cell proliferation, AKT, AKT phosphorylation	Chen et al., 2022

Table 2 continued.

-	Gastric cancer	BGC-823 and SGC-7901 cell lines, in vitro	0-16 µg/ml	3.63 ± 0.54 -19.83 ± 1.30 µM and 2.92 ± 0.34 -14.52 ± 0.89 µM	↑Apoptosis, Bax ↓Cell proliferation, migration, invasion, tumor growth, COX-2, PCNA, Bcl-2, MMP-2, xenograft growth	Zhang et al., 2014
		Male athymic nude mice, in vivo (n = 6)	15, 30 and 60 mg/kg (i.p.)			
-	Breast cancer	BT549-Twist-cell,4T1 cell lines, in vitro	5-20 µM and 60-180 µM	-	↑Twist1 degradation ↓Migration, invasion, cell proliferation, ZEB2, Bmi1, N-Cadherin, Vimentin,	Nafie et al., 2021
seeds of Peganum harmala	Colon cancer	SW620 cell line, in vitro	0-20.00 µg/ml	5.13 µg/ml	↑Cell cycle arrest, apoptosis, cytotoxicity, cyclin A, cdc2, Myt-1, p-cdc2, Bax,cell Proliferation, caspase-3,caspase-9 ↓Cell growth, cyclin D1, transmembrane potential, Bcl-2, Mcl-1,p-ERK, p-Akt, Akt, p-FoxO3, p-GSK3β	Liu et al., 2016
-	Gastric cancer	SGC-7901 cell line, in vitro	1-16 µg/ml	-	↑Apoptosis, Bax ↓Cell proliferation, COX-2, PCNA, Bcl-2, tumor growth	Yu et al., 2016
		Male athymic nude mice, in vivo (n=6)	30 mg/kg (i.p.)			
-	Breast cancer	MDA-MB-231 and MCF-7 cell lines, in vitro	0-150 µM		↑Apoptosis, Vimentin, N-cadherin, fibronectin ↓TAZ, EMT, metastasis, E-cadherin, nuclear localization, migration, invasion, growth, proliferation	He et al., 2022
-	Colon cancer	colon 26 cell line, in vitro	1-300 µg/mL	20.62 µg/mL	↑Apoptosis ↓Proliferation, migration, invasion, metastasis, VEGF, MMP 2, MMP 9, TGF-β, EMT, tumor growth	Li et al., 2020
		BALB/c male mice, in vivo (n=3)	30 mg/kg (t.v.)			
-	Thyroid Cancer	BHT-101 and CAL-62 cell lines, in vitro	0.1-100 µM	11.7 ± 308 µM and 22.0 ± 1.6 µM	↑Apoptosis, PARP-1, E-cadherin ↓Twist1 protein, fibronectin, migration, cell proliferation, cell growth	Baldini et al., 2024
-	Ovarian cancer	SKOV3, A2780 and ES2 cell lines, in vitro	0-30 µM	-	↑Autophagy, LC3-II/I, ATG5, Beclin1, ATGs, FOXO3, bilayer membrane density, Fe2+, ferroptosis, MDA, NARL3, casepase-1, IL-18, GSDMD, pyroptosis ↓p-mTOR, p-PI3K, p-AKT, mitochondrial volume, p62, lysosome, cristae, xCT, NRF2, GPX4, GSH, SOD, cell proliferation	Zhu et al., 2024
-	Gastric cancer	SGC-7901 and MKN-45 cell lines, in vitro	1 -16 µg/ml	-	↑Apoptosis ↓Cell proliferation, migration, invasion, MMP-9, COX-2 expression	Sun et al., 2015
Peganum Harmala	Blood cancer	NB4 cell line, in vitro	1.6-102.4 lg/ml	-	↑p15, DNA Methylation Cell Proliferation, DNMT1	Oodi et al., 2017
-	Breast cancer	MCF-7 cell line, in vitro	0-30 µM	-	↑Cytotoxicity, senescence, p53, p21 ↓Telomerase activity, hTERT mRNA expression, CDK2, c-Myc, cell growth, cell proliferation	Zhao and Wink, 2013
-	Liver cancer	HepG2 cell line, in vitro	3.3-270 µg/ml	60.02 ± 0.22 µg/ml	↓Tumor growth	Bei et al., 2014
		Female Balb/c mice, in vivo (n=10)	10 mg/kg (i.v.)			
Peganum harmala	Breast cancer	MDA-MB-231 cell line, in vitro	30 µg/ml	-	↑Apoptosis, Puma, Bax, Bid, TRAIL, Caspase-8, p53, p21 ↓Cell growth, Bcl-2	Hashemi Sheikh Shabani et al., 2015
-	Breast cancer	MDA-MB-231 and MCF-7 cell lines, in vitro	1.25- 40.00 µg/mL	-	↑Toxicity, fluorescence intensity, apoptosis ↓DNA topoisomerase II, cell cycle, cell proliferation	Tang et al., 2023

↑: increase; ↓: decrease; i.p.: intraperitoneal; LC3: the light chain 3; mTOR: mammalian target of rapamycin; PARP: poly-ADP-ribose polymerase; i.v.: intravenously; JNK: c-Jun N-terminal kinase; BCRP: Breast cancer resistance protein; MAO: monoamine oxidase; EGF: epidermal growth factor; VEGF: vascular endothelial growth factor; MMP: matrix metalloproteinase; PCNA: proliferating cell nuclear antigen; EMT: Epithelial-mesenchymal transition; COX-2: Cyclooxygenase-2; DNMT1: DNA methyl transferase 1; CDKs: cyclin-dependent kinases; s.b.: subcutaneously injected; t.v.:tail vein injected; TAZ: transcriptional coactivator with PDZ-binding motif; p-Erk: Phosphorylated extracellular signal-regulated kinase; p-Akt: Phosphorylated protein kinase B; Bcl-2: B-cell lymphoma 2; Cleaved-PARP: Cleaved Poly (ADP-ribose) polymerase; DYRK1A: Dual-Specificity Tyrosine Phosphorylation-Regulated Kinase 1A; c-Myc: cellular myelocytomatosis oncogene; PTEN: phosphatase and tensin homolog deleted on chromosome; ERK: extracellular signal-regulated kinase; CREB: cyclic adenosine monophosphate response element binding protein; ZEB2: Zinc Finger E-Box Binding Homeobox 2; Bmi1: B-Cell-Specific Moloney Murine Leukemia Virus Integration Site 1; Cdc2: Cell Division Cycle 2; Myt1: Membrane-associated tyrosine- and threonine-specific cdc2-inhibitory kinase; p-Cdc2: Phosphorylated Cell Division Cycle 2; p-FoxO3: Phosphorylated Forkhead box O3; p-GSK3β: Phosphorylated Glycogen Synthase Kinase 3 Beta; TGF: transforming growth factor; PARP: poly(ADP-ribose) polymerase; DNA: Deoxyribonucleic acid; hTERT: Human Telomerase Reverse Transcriptase; Fe²⁺: Ferrous ion; MDA: Malondialdehyde; NARL: NACHT, LRR, and PYD domains-containing protein; GSDMD: Gasdermin D; NRF: Nuclear factor erythroid 2; GPX4: Glutathione peroxidase 4; GSH: Glutathione; SOD: Superoxide dismutase; xCT: Cystine;

Table 3. Physicochemical and drug-likeness properties of harmine predicted by SwissADME

Category	Parameter	Value
Physicochemical Properties	Formula	C13H12N2O
	Molecular weight	212.25 g/mol
	Heavy atoms	16
	Aromatic heavy atoms	13
	Fraction Csp ³	0.15
	Rotatable bonds	1
	H-bond acceptors	2
	H-bond donors	1
	Molar refractivity	65.06
	TPSA	37.91 Å ²
Lipophilicity	Log P (iLOGP)	2.07
	Log P (XLOGP3)	3.74
	Log P (WLOGP)	3.03
	Log P (MLOGP)	1.56
	Log P (SILICOS-IT)	3.49
	Consensus Log P	2.78
Water Solubility	ESOL	Log S -4.05, 1.90e-02 mg/ml, 8.97e-05 mol/l, class Moderately soluble
	Ali	Log S -4.23, 1.25e-02 mg/ml, 5.91e-05 mol/l, class Moderately soluble
	SILICOS-IT	Log S -5.11, 1.66e-03 mg/ml, 7.80e-06 mol/l, class Moderately soluble
	GI absorption	High
Pharmacokinetics	BBB permeant	Yes
	P-gp substrate	No
	CYP1A2 inhibitor	Yes
	CYP2C19 inhibitor	No
	CYP2C9 inhibitor	No
	CYP2D6 inhibitor	No
	CYP3A4 inhibitor	Yes
	Log Kp (skin)	-4.94 cm/s
	Lipinski	Yes, 0 violation
Drug-likeness	Ghose	Yes
	Veber	Yes
	Egan	Yes
	Muegge	Yes
	Bioavailability score	0.55

proliferation and AKT phosphorylation, resulting in a reduction of colony formation (Chen et al., 2022). Additionally, an in vitro study in HepG2 cells (3.3-270 µg/ml) and an in vivo study in female Balb/c mice (10 mg/kg (i.v.)) showed that HRM significantly inhibits tumor growth (Bei et al., 2014).

3.2.7 Lung cancer

Lung cancer's high death rate worldwide poses a serious risk to public health (de Groot et al., 2012). Lung cancer is mostly caused by tobacco consumption, which includes cigarette smoking, pipes, and nicotine, though it can also strike nonsmokers. Preexisting chronic lung disorders, contact with airborne pollutants, hereditary susceptibility to cancer, indirect smoke exposure, and occupational hazards such as chemicals, radon, and asbestos fibers are additional risk factors (Gupta et al., 2023; Alshehabi, 2017). Advances in the

genetics of lung cancer may lead to customized therapies that target specific genes and pathways. The main signaling channels that could provide therapy roadmaps are as follows: pathways that stimulate development (Ras/epidermal growth factor receptor/phosphatidylinositol 3 kinase), inhibit growth (p53/Rb/P14ARF, STK11), trigger apoptosis (Bcl-2/Bax/Fas/FasL), fix DNA, and immortalize genes (Bhuia et al., 2023b; Brambilla and Gazdar, 2009; Shtivelman et al., 2014). Chen et al. (2005) expressed that HRM at 40 µg/ml induced apoptosis in HepG2 and S180 cells (IC₅₀: 0.011–0.021 µmol/ml) by activating Fas and mitochondrial pathways while inhibiting topoisomerases I/II, microtubule formation, and Bcl-2 (Chen et al., 2005). In C₅₇BL/6 mice (n=8), HRM at 7.5 mg/kg (i.v.) exhibits significant anticancer activity by downregulating tumour growth (Chen et al., 2005).

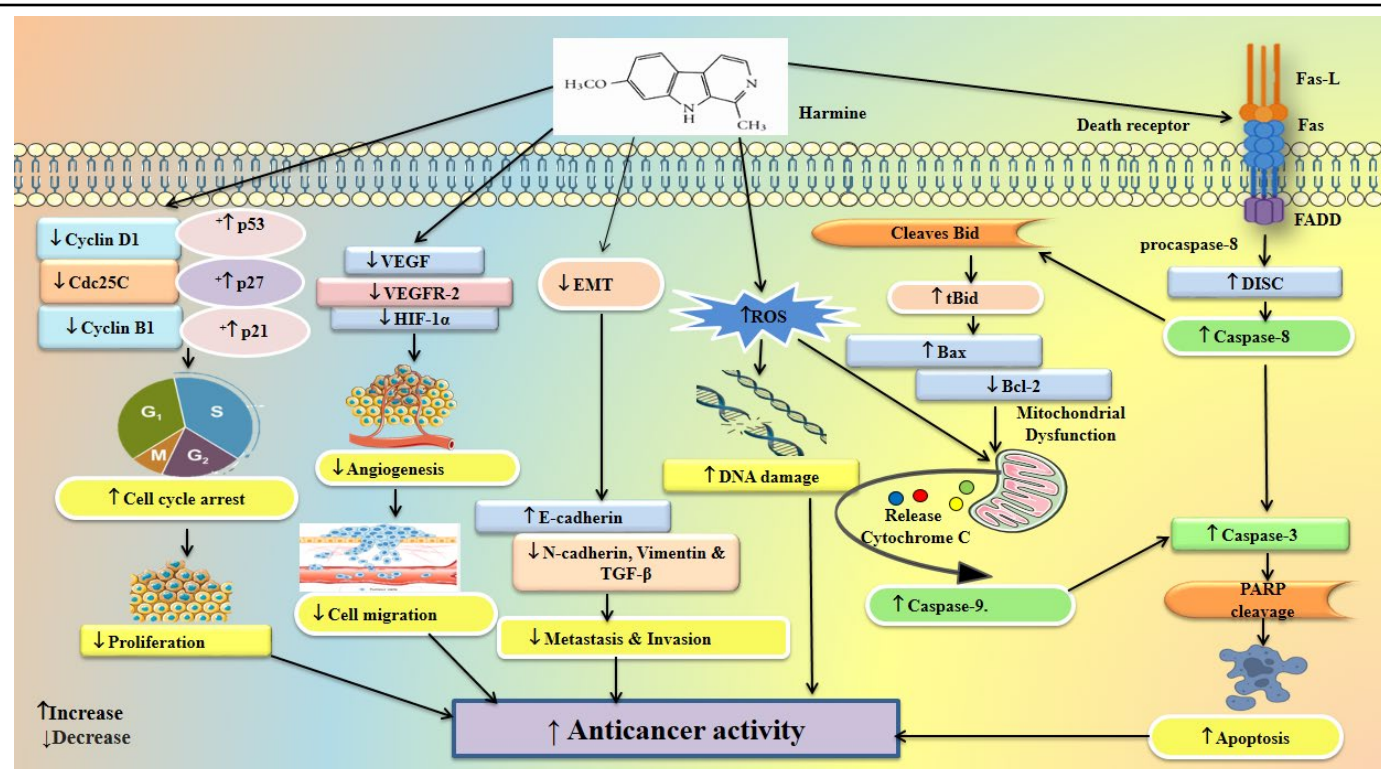


Figure 1. Possible mechanism of anticancer activity of harmine. [The image illustrates the anticancer mechanism of HRM, highlighting its effects on various cellular pathways. HRM induces cell cycle arrest by upregulating p53, p27, and p21, while downregulating Cyclin D1, Cyclin B1, and Cdc25C, leading to reduced cancer cell proliferation. Additionally, it suppresses angiogenesis by downregulating VEGF, VEGFR-2, and HIF-1α, thereby reducing blood vessel formation and cell migration. HRM also inhibits EMT by increasing E-cadherin and reducing N-cadherin, Vimentin, and TGF-β, which helps prevent metastasis and invasion. Furthermore, it promotes the generation of ROS, leading to increased DNA damage, which contributes to cancer cell death. HRM increases Bax and decreases Bcl-2, causing mitochondrial dysfunction and cytochrome C release. This activates caspase-9 and caspase-3, leading to PARP cleavage and apoptosis. p53: Tumor Protein p53; p27: Cyclin-Dependent Kinase Inhibitor 1B (CDKN1B); p21: Cyclin-Dependent Kinase Inhibitor 1A (CDKN1A); Cyclin D1: G₁/S-Specific Cyclin-D1; Cyclin B1: G₂/M-Specific Cyclin-B1; Cdc25C: Cell Division Cycle 25C; VEGF: Vascular Endothelial Growth Factor; VEGFR-2: Vascular Endothelial Growth Factor Receptor-2; HIF-1α: Hypoxia-Inducible Factor-1 Alpha; EMT: Epithelial-Mesenchymal Transition; E-cadherin: Epithelial Cadherin; N-cadherin: Neural Cadherin; TGF-β: Transforming Growth Factor Beta; ROS: Reactive Oxygen Species; Bax: Bcl-2-Associated X Protein; Bcl-2: B-cell Lymphoma 2; Caspase-9: Cysteine Aspartate-Specific Protease-9; Caspase-3: Cysteine Aspartate-Specific Protease-3; PARP: Poly (ADP-Ribose) Polymerase;].

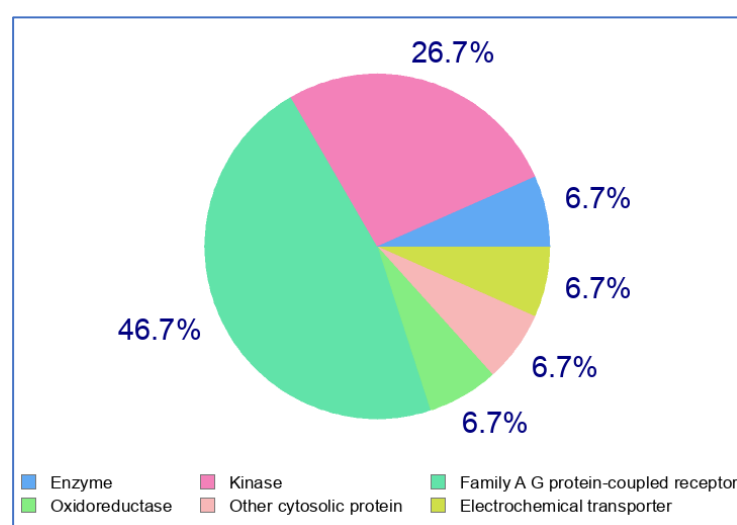


Figure 2. The pie chart illustrates the distribution of harmine's predicted protein target classes based on in silico analysis using SwissTargetPrediction. The majority of targets were classified as Family A G protein-coupled receptors (46.7%), followed by kinases (26.7%), with smaller proportions attributed to enzymes, oxidoreductases, electrochemical transporters, and cytosolic proteins (each 6.7%). These results suggest harmine's potential to act through multiple molecular pathways relevant to cancer therapy.



Figure 3. Predicted Toxicity and Target Interaction Profile of Harmine (ProTox-II). The radar plot shows harmine's predicted toxicity risks and molecular target interactions using ProTox-II. High probabilities were observed for hepatotoxicity (100%) and neurotoxicity (83%), along with strong interaction with CYP2E1 and moderate effects on other CYP enzymes. Notable interactions with androgen and estrogen receptors suggest potential endocrine effects. These in silico results indicate multitarget activity with possible safety concerns.

3.2.8 Ovarian cancer

Ovarian cancer is a common disease in women and accounts for the majority of gynecologic cancer-related deaths (Zhang et al., 2022). Risk variables include age, early menarche, late menopause, surroundings, and family history (Salehi et al., 2008). Among them, epigenetic and genetic factors are considered the most important of these, while pregnancy and nursing lower this risk (Rooth, 2013). Cyto-reductive surgery as well as cisplatin-based chemotherapy are the mainstays of treatment for patients suffering from advanced ovarian cancer, who have the worst prognosis in terms of curative therapeutic choices. However, a large number of patients exhibit innate or learned immunity to cisplatin-based treatment plans (Pecorelli et al., 2002; Pokhriyal et al., 2019). HRM demonstrated strong anticancer activity against various ovarian cancer cells in both in vitro and in vivo models. Gao et al. (2017) said that HRM reduced SKOV-3 (0–30 μ M) ovarian cancer cell proliferation, migration, and colony formation by inhibiting ERK1/2 phosphorylation, CREB activity, and important growth markers like PCNA, EGF, VEGF, MMP-2, and MMP-9 (Gao et al., 2017). Another study by Zhu et al. (2024) investigated that HRM (0–30 μ M) increased autophagy, ferroptosis, and pyroptosis in SKOV3, A2780, and ES2 ovarian cancer cells via upregulating LC3-II/I, ATGs, FOXO3, and caspase-1 while decreasing p-mTOR, p-PI3K,

p-AKT, xCT, NRF2, and GPX4, which led to suppression of cell proliferation (Zhu et al., 2024).

3.2.9 Pancreatic cancer

Pancreatic ductal carcinoma is a type of carcinoma that develops from the cells covering the pancreatic duct (Kleeff et al., 2016). At the moment, it ranks as the fourth most common cause of mortality linked to cancer. It is anticipated to become the second most common cause of cancer-related fatalities by 2030, though, because of its aggressive nature (Muniraj et al., 2013; Park et al., 2021). According to the study, HRM (0–40 μ M) displayed significant anticancer activity against pancreatic cancer cells PANC-1, CFPAC-1, SW-1990, and BxPC-3, increasing apoptosis, p21, cyclin B1, caspase-3 activation, and trabecular bone mass while suppressing colony formation, proliferation, c-Myc, and the AKT/mTOR pathway (Wu et al., 2019).

3.2.10 Skin cancer

Skin cancer is the uncontrolled growth of abnormal skin cells, often caused by ultraviolet radiation exposure. It includes types like basal cell carcinoma, squamous cell carcinoma, and melanoma, with melanoma being the most aggressive form (Mancebo and Wang, 2014; Linares et al., 2015). Skin cancer is one of the most common cancers worldwide, with over 1.5 million new cases annually (Arnold et al., 2022). A study by Hamsa et al. (2011) said that HRM exhibits an anti-cancer effect against B16F-10 skin cancer cells (0.5–

2 µg/mL) by triggering apoptosis via upregulation of Bax, p53, Caspase-3, -8, -9, and Bid. It also inhibits Bcl-2 and cell growth.

3.2.11 Thyroid cancer

Thyroid cancer is a common endocrine tumor, and research into its molecular causes has advanced significantly in recent years (Xing, 2013). Radiation exposure, iodine consumption, obesity, estrogen, debates, reproductive variables, Hashimoto's thyroiditis, and lifestyle factors are among the risk factors for thyroid cancer (Kruger et al., 2022). Thyroid gland surgery, tyrosine kinase inhibitor-based molecular-targeted therapy, and radioactive iodine treatment are among the treatment options available to patients who have thyroid cancer (Silaghi et al., 2022). In our study, Ruan et al. (2017) investigated that, in TPC-1 cells, HRM at 2-64 µg/mL significantly increased apoptosis and cytotoxicity as well as decreased cell proliferation, colony formation, migration, and invasion by upregulating Bax and Caspase-3 and downregulating Bcl-2 (Ruan et al., 2017). Additionally, an in vivo study by Ruan et al. (2017) showed that, in C₅₇BL/6 mice, HRM at 7.5 mg/kg (i.v.) significantly inhibits cell growth (Ruan et al., 2017). Another study also said that HRM (0.1-100 µM) promoted apoptosis, increased PARP-1 and E-cadherin, and inhibited Twist1, fibronectin, migration, proliferation, and growth in BHT-101 and CAL-62 thyroid cancer cells (Baldini et al., 2024).

Our overall result showed that HRM expressed a significant effect against several cancers, including lung cancer, skin cancer, and blood cancer. It triggered apoptosis by activating several factors such as caspase 8, 9, and 3, Bax while reducing cell proliferation, colony formation capacity, migration, and invasion. Several in vitro studies showed that HRM increased cytotoxicity toward different cancer cell lines. These results emphasize HRM's possibility as a therapeutic drug that regulates important processes associated with tumor formation. Further research should focus on improving its pharmacokinetic features in order to improve effectiveness.

However, the anticancer activity of HRM across various cancers, as reported in the literature, is summarized in Table 2, while its possible mechanism of action is illustrated in Figure 1.

4. In Silico Analysis

4.1 Predicted Protein Target Classes of Harmine

The in-silico target prediction of harmine revealed a diverse range of molecular target classes, suggesting its potential as a multi-target anticancer agent. According to the pie chart analysis, the largest proportion (46.7%) of predicted targets belonged to the Family A G protein-coupled receptors (GPCRs). GPCRs are known to regulate multiple signaling pathways related to cell survival, proliferation, angiogenesis, and immune modulation in cancer cells (Doostmohammadi et al., 2024). The high percentage of GPCR-related targets indicates that harmine may interfere with tumor cell signaling, possibly by blocking or modulating GPCR-mediated

oncogenic pathways, which are often overactivated in various cancer types (Figure 2).

The second major class, comprising 26.7%, was protein kinases, which are well-established targets in modern cancer therapy. Kinases regulate key events in cell cycle progression, apoptosis, and metastasis (Lupan et al., 2024). Harmine has been previously shown to inhibit cyclin-dependent kinases (CDKs), particularly Cdk2, through phosphorylation inactivation, leading to cell cycle arrest at the G2 phase (Ock & Kim, 2021). Therefore, its interaction with other kinases further strengthens its potential as a kinase-targeting anticancer compound.

Interestingly, the remaining 6.7% targets were distributed among several functionally important protein classes: enzymes, oxidoreductases, electrochemical transporters, and other cytosolic proteins. These groups are involved in critical cellular processes such as redox balance, energy metabolism, and intracellular transport. For instance, oxidoreductases are involved in regulating oxidative stress, which is a key contributor to cancer progression and drug resistance (M et al., 2022). Harmine's possible influence on oxidative stress pathways may therefore contribute to its pro-apoptotic effects.

Moreover, the presence of electrochemical transporters as predicted targets may indicate harmine's potential to interfere with ion homeostasis or membrane transport, which are also emerging areas in cancer drug discovery. The targeting of cytosolic proteins suggests that harmine may modulate intracellular signaling or interact with downstream effectors beyond the membrane receptors.

Taken together, these findings suggest that harmine does not act through a single linear mechanism, but rather exhibits pleiotropic effects by engaging with multiple classes of proteins involved in cancer pathogenesis. This polypharmacological profile supports its use as a lead compound for developing multi-target anticancer therapies, especially in complex tumors where monotherapy often fails due to resistance or redundancy in signaling pathways.

4.2 Physicochemical and Drug-Likeness Profile of Harmine

The physicochemical profile of harmine (Table 3), analyzed using SwissADME, indicates its potential suitability as an orally active drug. Harmine has a molecular formula of C₁₃H₁₂N₂O and a molecular weight of 212.25 g/mol, which falls well within the acceptable range for drug-like molecules (Lipinski et al., 2001). It contains 13 aromatic heavy atoms, only 1 rotatable bond, and shows a low fraction of sp³ carbon atoms (0.15), suggesting a rigid planar structure—a characteristic that often favors strong binding to biological targets (Meyer et al., 2003). The TPSA (Topological Polar Surface Area) is 37.91 Å², which is below the 140 Å² threshold for good intestinal absorption and blood-brain barrier (BBB) permeability (Remko et al., 2011).

In terms of lipophilicity, harmine shows a consensus Log P of 2.78, calculated from five prediction models. This balanced lipophilicity supports its ability to cross lipid membranes, yet remain soluble enough in aqueous environments (Fahr et al., 2005). The water solubility analysis (Log S values ranging from -4.05 to -5.11) categorizes harmine as moderately soluble, which is acceptable for oral formulations. These properties altogether suggest a favorable absorption profile, making it a viable candidate for further formulation development.

Harmine also shows high gastrointestinal (GI) absorption and the ability to penetrate the blood-brain barrier, indicating possible effects on both peripheral and central targets. It is not a P-glycoprotein substrate, which may enhance its intracellular retention. Interestingly, harmine is predicted to inhibit CYP1A2 and CYP3A4, key enzymes involved in drug metabolism (Zhao et al., 2011). This raises the possibility of drug-drug interactions, which should be considered in future pharmacokinetic studies. The compound complies with all five major drug-likeness filters-Lipinski, Ghose, Veber, Egan, and Muegge rules-with zero violations, further supporting its candidacy as a lead compound (Sukhachev et al., 2024). The bioavailability score of 0.55 suggests moderate oral bioavailability.

Overall, harmine exhibits a strong drug-like profile, with favorable lipophilicity, solubility, permeability, and bioavailability characteristics. These properties, along with its previously reported anticancer and kinase-inhibiting activities, make harmine a promising candidate for further development as an anticancer therapeutic. However, its CYP inhibition potential and BBB permeability also point to the need for careful toxicity and safety evaluation in vivo.

4.3 Toxicological Profile

Toxicological analysis is a crucial phase in the drug development process because it guarantees the safety of novel treatment candidates and averts potential harm along with side effects prior to use in clinical trials (Dorato and Buckley, 2006). HRM functions as a bioactive component present in a number of well-known medicinal plants that have long been used in conventional medicine (Javeed et al., 2018). However, despite their advantageous pharmacological properties, some natural materials can have adverse effects as well as prominent toxicity in some circumstances, according to studies of the ingredients in conventional drugs and contemporary pharmacology research (Zhong et al., 2022). HRM acts as a reversible inhibitor of monoamine oxidase A (MAO-A), an enzyme responsible for breaking down neurotransmitters such as serotonin, dopamine, and norepinephrine (Figure 3). By inhibiting MAO-A, HRM increases the levels of these neurotransmitters in the brain, which contributes to its psychoactive effects but also poses risks of toxicity, particularly at high doses (Benny et al., 2023). Acute toxicity studies indicate that HRM has a median lethal dose

(LD50) of approximately 120 mg/kg in mice when administered intraperitoneally, with symptoms of overdose including tremors, convulsions, hyperthermia, and respiratory distress (Frecska et al., 2016). HRM also interacts with other drugs, particularly serotonergic agents, increasing the risk of serotonin syndrome, a potentially life-threatening condition (Brito-da-Costa et al., 2020). Furthermore, HRM may inhibit cytochrome P450 enzymes, altering the metabolism of co-administered drugs and potentially leading to adverse effects (Herraiz et al., 2010). Chronic use of HRM may lead to neurotoxicity and hepatotoxicity, although these effects are not well-documented in humans. Additionally, HRM ability to intercalate into DNA raises concerns about its genotoxic potential, though evidence of carcinogenicity remains limited (Pfau and Skog, 2004).

4.4 Clinical evidence

A clinical study is a crucial step in the research process for creating a new drug, which is described as examinations or trials conducted on human subjects (Friedman et al., 2015). Clinical trials are crucial for the detection, diagnosis, and prevention of disease and also for the creation of innovative treatment strategies (Piantadosi, 2024). Clinical studies also provide information on accuracy, safety, and evidence-based treatment (Friedman et al., 2015). HRM demonstrated potential therapeutic effects in preclinical and clinical studies, particularly in neurodegenerative and psychiatric disorders. HRM has the ability to inhibit monoamine oxidase A (MAO-A), which enhances serotonin and dopamine levels, which may benefit conditions like depression (Prinsloo, 2019). A study by Morales-García et al. (2017) highlighted HRM's neurogenic properties, promoting hippocampal neurogenesis, which could be beneficial for Alzheimer's disease (Morales-García et al., 2017). Additionally, HRM has shown anticancer activity by targeting dual-specificity tyrosine phosphorylation-regulated kinases (DYRK1A) in pancreatic cancer cells (Kumar et al., 2018). In 2021, Mount Sinai researchers received FDA approval to conduct a Phase 1 clinical trial assessing HRM's safety and tolerability in healthy volunteers (Ables et al., 2024). These findings suggest that harmine could be a viable candidate for therapies aimed at beta-cell regeneration in diabetes patients. Despite promising results, further clinical trials are needed to establish its safety and efficacy in humans.

5. Conclusion

This review demonstrates that harmine (HRM) is a potent natural compound with significant anticancer activity against a wide range of cancers, including breast, colon, liver, lung, thyroid, skin, and hematological malignancies. Harmine acts through multiple mechanisms such as cytotoxicity, apoptosis induction, cell cycle arrest, inhibition of cell proliferation and migration, autophagy activation, and promotion of oxidative stress. Among these, its pro-apoptotic and cell cycle regulatory effects have been most

consistently reported. While some dose-dependent toxicities—such as hepatotoxicity, neurotoxicity, and inhibition of cytochrome P450 enzymes—have been observed, harmine's multi-targeted actions and favorable drug-like properties support its candidacy as a promising anticancer agent.

6. Future Directions

To fully realize harmine's therapeutic potential, further research is essential. Future studies should focus on comprehensive *in vitro* and *in vivo* preclinical experiments, including dose optimization, safety profiling, and mechanistic studies. Given harmine's inhibitory effect on CYP450 enzymes, careful pharmacokinetic and drug-interaction studies are also needed to ensure safety in polypharmacy settings. Additionally, well-designed clinical trials are crucial to evaluate its efficacy, toxicity, and pharmacodynamics in human subjects. With rigorous validation, harmine could be developed into an effective, affordable, and multi-mechanistic anticancer drug with fewer side effects than conventional chemotherapy.

Author contributions

NTY contributed to literature collection, data extraction, and preliminary drafting of the manuscript. MNHS assisted in database searching, study screening, and organization of experimental and mechanistic evidence. MEH contributed to data interpretation, toxicological assessment, and critical evaluation of pharmacological findings. MSAH conceptualized and supervised the study, designed the review framework, validated the methodology, and performed critical revision of the manuscript. MTR conducted the *insilico* analyses (SwissADME and ProTox-II) and assisted in interpretation of pharmacokinetic and toxicity data. EM supported manuscript editing, figure/table verification, and reference management.

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Competing financial interests

The authors have no conflict of interest.

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