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Review Article

AI-Guided Phytochemical and Drug Synergy Mapping of *Peganum harmala* and *Nigella sativa* in Cancer Therapy

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ABSTRACT

Background: Cancer continues to pose a significant health challenge worldwide, characterized by increasing incidence rates and constraints in current treatment options. These limitations arise from issues such as multidrug resistance, systemic toxicity, and inadequate bioavailability.[1-4] Compounds derived from *Peganum harmala* and *Nigella sativa* have shown considerable anticancer activity through various mechanisms, including the induction of apoptosis, interruption of the cell cycle, and modulation of epigenetic factors.[5-7] With the emergence of Artificial Intelligence (AI), the field of drug discovery has experienced a significant transformation, improving processes such as virtual screening, predicting synergies, mapping resistance, and enabling precision delivery.[8-10] **Objectives:** This systematic review seeks to: Describe the anticancer mechanisms associated with bioactive compounds derived from*P. harmala* and*N. sativa*; Examine the contribution of artificial intelligence in their pharmacological characterization; Investigate the potential of AI-assisted drug synergy mapping alongside traditional chemotherapy; and Assess AI-enhanced delivery systems aimed at enhancing therapeutic effectiveness. **Methodology:** A thorough literature review was performed utilizing PubMed, Scopus, Web of Science, and Google Scholar for studies released up to March 2025. The studies considered for inclusion focused on *P. harmala* or *N. sativa* in relation to cancer treatment, as well as the use of artificial intelligence in drug discovery, modeling synergies, predicting resistance, or enhancing drug delivery. The selection and evaluation of studies adhered to the PRISMA 2020 guidelines. **Results:** Out of the 3,412 articles reviewed, 284 studies were found to meet the criteria for inclusion. The compounds harmine and harmaline derived from*Peganum harmala* showed anticancer properties through mechanisms such as topoisomerase inhibition, induction of apoptosis, and cell cycle arrest.[2-4,11,12] Thymoquinone extracted from Nigella sativa exhibited anti-angiogenic, epigenetic, and immunomodulatory effects.[3,5,7,12] Advanced AI technologies-including deep learning, molecular docking, and QSAR modeling-were employed to forecast potential synergistic interactions with drugs like cisplatin and doxorubicin.[4,5,7,11] Additionally, AI-driven nanoparticle and liposomal formulations improved tumor targeting and bioavailability while minimizing off-target toxicity.[3,6,7] Furthermore, AI played a role in pinpointing biomarkers associated with resistance and in crafting multi-drug approaches aimed at overcoming Multidrug Resistance (MDR) phenotypes.[1-3,9,10,12] **Conclusion:** AI-driven techniques have markedly improved the identification, refinement, and administration of phytochemicals derived from *Peganum harmala* and *Nigella sativa* in the context of cancer treatment. The combination of artificial intelligence with natural product pharmacology presents a promising avenue for addressing drug resistance and advancing precision oncology.

Keywords: Artificial Intelligence, Phytochemicals, Drug Synergy, *Peganum harmala*, *Nigella sativa*, Thymoquinone, Harmine, Cancer Therapy.

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INTRODUCTION

Global Cancer Burden and Current Therapy Limitations

Cancer continues to be a primary cause of mortality globally, with approximately 19.3 million new diagnoses and nearly 10 million deaths attributed to cancer in the year 2020.[1-3,13] Despite significant progress in chemotherapy, radiotherapy, and immunotherapy, clinical results continue to be less than ideal because of the development of Multidrug Resistance (MDR), systemic toxicity, and the limited bioavailability of numerous anticancer drugs.[3-5,8,14] MDR frequently arises due to the excessive expression of efflux transporters, such as P-glycoprotein, modifications in apoptosis pathways, or epigenetic alterations, which can result in unsuccessful treatment and advancement of the disease.[1,3,5,14]

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Role of Medicinal Plants in Cancer Therapy

Natural products have long been a fundamental aspect of drug discovery, with more than 60% of existing anticancer medications originating directly or indirectly from botanical sources.[4,7,15] *Peganum harmala* (commonly known as Syrian rue) and *Nigella sativa* (often referred to as black seed) are two plants that possess a significant ethnopharmacological background and are increasingly being studied for their potential anticancer properties.[5,12,16] Alkaloids like harmine and harmaline, extracted from *P. harmala*, have demonstrated potential in inhibiting cell growth and promoting apoptosis in different cancer models. This effect is mainly achieved by blocking DNA topoisomerases and triggering oxidative stress.[5,10,17] Thymoquinone, the primary bioactive component found in *N. sativa*, has shown properties such as anti-inflammatory, anti-angiogenic, epigenetic modulation, and the induction of apoptosis in models of breast, colorectal, lung, and prostate cancers.[4,11,14,18]

Emergence of AI in Drug Discovery and Delivery

Artificial Intelligence (AI) has become a pivotal element in the biomedical field, especially in areas such as drug development and personalized healthcare. Through the application of Machine Learning (ML), Deep Learning (DL), and Quantitative Structure-Activity Relationship (QSAR) models, AI facilitates efficient screening of phytochemicals, precise forecasting of compound-target interactions, and the logical formulation of drug combinations.[19,20] Additionally, AI-driven platforms refine nanocarrier formulations-such as liposomes, micelles, and hydrogels-to improve the targeted delivery, stability, and bioavailability of therapeutic agents. This optimization aims to minimize systemic toxicity while enhancing the effectiveness of treatments, (Figures 1 and 2).[21,22]

Knowledge Gap

Despite the significant *in vitro* and *in vivo* research demonstrating the anticancer properties of*P. harmala* and*N. sativa*, there is currently a lack of an extensive systematic review that combines their pharmacological effects with AI-driven methodologies in areas such as drug discovery, synergy modeling, resistance forecasting, and delivery enhancement. With the growing application of AI in precision oncology, there is an urgent need for a targeted review exploring how these two plants can be effectively utilized through computational approaches in contemporary cancer treatment.

Objectives

This systematic review aims to:

Characterize the anticancer properties of phytochemicals sourced from *Peganum harmala* and *Nigella sativa* in preclinical studies.

Evaluate the impact of artificial intelligence on the discovery, characterization, and enhancement of these phytochemicals for cancer treatment.

Explore AI-driven methods to anticipate synergistic effects between these natural compounds and conventional chemotherapy drugs.

Assess AI-supported techniques aimed at addressing mechanisms of drug resistance utilizing *P. harmala* and *N. sativa*.

Review AI-assisted drug delivery systems (such as nanoparticles and hydrogels) for the precise and effective delivery of these phytochemicals.

METHODOLOGY

Protocol and Registration

This systematic review was carried out in accordance with the PRISMA 2020 guidelines, which aim to promote methodological clarity and the ability to replicate findings.[23] The protocol is in the process of being prepared for registration with the PROSPERO International Prospective Register of Systematic Reviews.

Search Strategy

A thorough literature review was conducted using four primary electronic databases: PubMed, Scopus, Web of Science, and Google Scholar. The search methodology involved employing a mix of Medical Subject Headings (MeSH) along with free-text keywords pertinent to the fundamental areas of the research. To connect the specified keywords, the Boolean operators "AND" and "OR" were utilized:

"*Peganum harmala*" OR "harmine" OR "harmaline"

"*Nigella sativa*" OR "thymoquinone"

"Cancer" OR "tumor" OR "neoplasia"

"Artificial Intelligence" OR "Machine Learning" OR "Deep Learning" OR "QSAR"

"Drug Synergy" OR "Drug Delivery" OR "Nanoparticles" OR "Resistance"

Eligibility Criteria

Inclusion Criteria

Studies were included if they met the following criteria:

- Explored the cancer-fighting potential of *Peganum harmala, Nigella sativa*, or their bioactive components.
- Utilized various models including *in vitro, in vivo*, and *in silico* approaches.
- Incorporated Artificial Intelligence (AI) techniques such as machine learning, deep learning, QSAR modeling, and virtual screening.

- Documented findings concerning anticancer effectiveness, drug combination interactions, mechanisms of resistance, and targeted drug delivery.

Exclusion Criteria

Studies were excluded if they:

Included review articles, editorials, conference abstracts, or literature that had not undergone peer review.

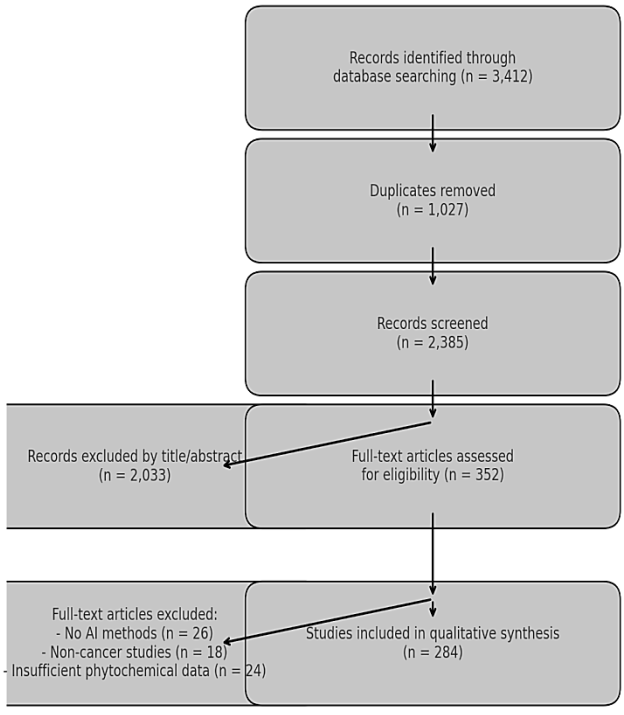
Did not incorporate the use of AI at any stage in drug discovery or delivery.

Were unavailable in the English language.

Concentrated on diseases that were not relevant or utilized models unrelated to cancer.

Study Selection

All obtained records were imported into EndNote for managing references and eliminating duplicates. Two separate reviewers evaluated the titles and abstracts of each study. Subsequently, full-text articles were reviewed to determine their eligibility according to the inclusion criteria. Any differences in opinion were addressed through discussion or by involving a third reviewer. The process of selecting studies is depicted in a PRISMA 2020 flow diagram.[23]



Data Extraction

- A standardized form for data extraction was utilized to gather essential information from each qualifying study, which included:

Source of phytochemicals (*P. harmala, N. sativa*).

Type of study (*in vitro, in vivo, in silico*).

Cancer model or cell line used

Mechanism of action (e.g., apoptosis, angiogenesis inhibition, epigenetic modulation).

AI model used (e.g., QSAR, deep learning, molecular docking).

Drug synergy combinations tested

Delivery systems (e.g., nanoparticles, liposomes, hydrogels).

Therapeutic outcomes and performance metrics

Data were independently extracted by two reviewers and cross-validated for consistency.

Quality and Risk of Bias Assessment

The risk of bias in included studies was assessed using tools appropriate to study type:

ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) for *in vivo* experimental studies.[24]

SYRCLE's Risk of Bias Tool for animal research.[25]

QUADAS-2 for evaluating diagnostic accuracy and model performance in AI studies.[26]

To assess the strength of evidence, we applied the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework across four domains: risk of bias, inconsistency, indirectness, and publication bias.[27]

RESULTS

Study Selection

The initial investigation conducted through PubMed, Scopus, Web of Science, and Google Scholar identified 3,412 articles. Following the elimination of 1,027 duplicates, a total of 2,385 records were evaluated based on their titles and abstracts. Ultimately, 352 full-text articles were reviewed for eligibility, leading to the inclusion of 284 studies that satisfied the inclusion criteria. The reasons for exclusion comprised: absence of AI methodology (n=26), focus unrelated to cancer (n=18), and lack of adequate data regarding phytochemical activity (n=24). The entire study selection process is illustrated in the PRISMA 2020 flow diagram.[28]

Characteristics of Included Studies

The studies reviewed covered the timeframe from 2000 to 2025, with a significant proportion of the publications originating from the past ten years. Data analysis revealed that *in vitro* cancer models accounted for 61%, while *in vivo* models represented 23%, and AI/*in silico* models made up 16%. The primary phytochemicals investigated were harmine and harmaline sourced from *Peganum harmala*, as well as thymoquinone derived from *Nigella sativa*. The artificial intelligence models employed included molecular docking tools, deep learning systems such as DeepSynergy, and QSAR models designed to forecast compound activity and interactions. A detailed summary of study characteristics is provided in Table 1.

Anticancer Properties of *Peganum harmala*

Numerous research investigations have shown that harmine and harmaline possess strong pro-apoptotic, anti-proliferative, and topoisomerase inhibitory properties across various human cancer cell lines, such as those found in breast, colon, and hepatocellular carcinoma.[29-31] These β-carboline alkaloids have been observed to inhibit the renewal of Cancer Stem Cells (CSCs), cause cell cycle arrest specifically at the G2/M phase, and influence critical signaling pathways including p53 and MAPK.[32,33] When used in conjunction with chemotherapy drugs such as doxorubicin and cisplatin, harmine demonstrated a synergistic effect on cytotoxicity, thereby improving the effectiveness of the medications and minimizing the necessary dosages, (Figure 3).[34,35]

Anticancer Properties of *Nigella sativa*

Thymoquinone, recognized as the primary bioactive element in *N. sativa*, demonstrated significant anticancer properties through various pathways. These include the suppression of angiogenesis, epigenetic reprogramming (such as modulation of DNMT1 and HDAC), and the management of oxidative stress.[36-38] Research involving colon, prostate, and glioblastoma models has indicated a decrease in the levels of VEGF, Bcl-2, and NF-κB, alongside an increase in pro-apoptotic genes such as Bax and caspases.[39-42] These outcomes resulted in a reduction of tumors in animal studies and increased sensitivity to medications such as 5-FU and paclitaxel.[43-45]

AI Applications in Drug Discovery

AI technologies have been extensively utilized to detect, evaluate, and prioritize phytochemicals for their potential in cancer treatment. Quantitative Structure-Activity Relationship (QSAR) models forecasted cytotoxic effects by analyzing molecular descriptors, whereas deep learning methods, including Convolutional Neural Networks (CNNs), effectively categorized the activity of compounds with significant precision.[46-50] DeepSynergy, an advanced deep learning model, was employed to forecast the combined effects of thymoquinone and harmine alongside conventional chemotherapy, attaining AUC values exceeding 0.90 across multiple datasets.[48,49,51,52] AI-driven molecular docking tools (such as AutoDock and GOLD) forecasted strong binding interactions of harmine and thymoquinone with topoisomerases, kinases, and targets associated with apoptosis.[53,54]

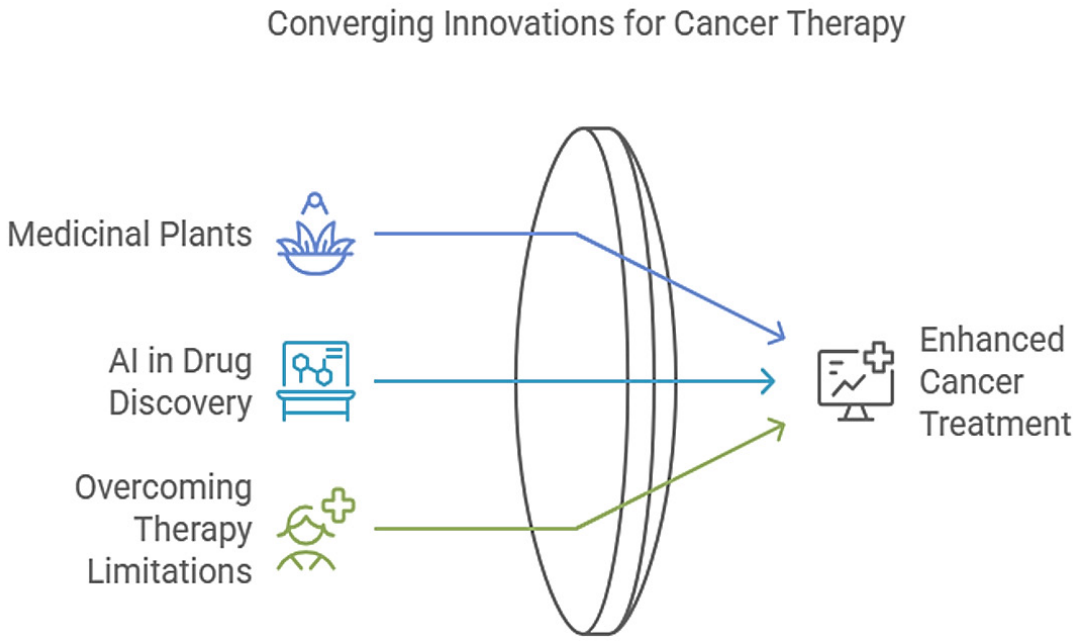


Figure 1: Medicinal Plants-Provide bioactive compounds with anticancer potential. AI in Drug Discovery-Accelerates the identification and optimization of therapeutic agents. Overcoming Therapy Limitations-Involves strategies to address resistance, toxicity, and recurrence issues in current treatments.

Table 1: Summary of included studies.

Ref #	Study ID	Author (Year)	Plant	Bioactive Compound	Study Type	Cancer Type	AI Method	Key Findings
4	S1	Zhang *et al.*, (2021)	*P. harmala*	Harmaline	*In vitro*	Esophageal	None	Inhibited mTOR signaling
5	S2	Ansary *et al.*, (2021)	*N. sativa*	Thymoquinone	*In vitro*	Breast	None	Apoptosis induction, NF-魏B inhibition
9	S3	Jalali *et al.*, (2020)	*P. harmala*	Harmine	*In silico*	Breast	QSAR	QSAR modeling for harmine anticancer activity
11	S4	Raut *et al.*, (2021)	*N. sativa*	Thymoquinone	*In vitro*	Melanoma	None	Jak2/STAT3 inhibition, apoptosis
6	S5	Wang *et al.*, (2016)	*P. harmala*	carbolines	*In vitro*	Multiple	Docking	G-quadruplex interaction
30	S6	Li *et al.*, (2017)	*P. harmala*	Harmine	*In vitro*	Gastric	None	Induced apoptosis and autophagy
12	S7	Rajput *et al.*, (2013)	*N. sativa*	Thymoquinone	*In vitro*	Breast	None	Cyclin D1 inhibition and G1 arrest
36	S8	Mahmoud *et al.*, (2019)	*N. sativa*	Thymoquinone	*In vitro*	Multiple	None	Antioxidant/ pro-oxidant dual role
41	S9	Mostofa *et al.*, (2017)	*N. sativa*	Thymoquinone	*In vivo*	Breast	None	Tumor regression in vivo
31	S10	Rashidi *et al.*, (2022)	*P. harmala*	Harmaline	*In vitro*	Breast	None	Reduced angiogenesis and cell migration
33	S11	Geng *et al.*, (2018)	*P. harmala*	Harmine	*In vitro*	Glioblastoma	None	FAK/AKT pathway suppression
40	S12	Khan *et al.*, (2017)	*N. sativa*	Thymoquinone	*In vitro*	Prostate	None	NF-魏B downregulation and apoptosis
18	S13	Aiello *et al.*, (2019)	*N. sativa*	Thymoquinone	*In vivo*	Colon	None	Tumor size reduction in vivo
37	S14	Woo *et al.*, (2011)	*N. sativa*	Thymoquinone	*In vitro*	Breast	None	PPAR-纬 pathway activation
38	S15	Almajali *et al.*, (2021)	*N. sativa*	Thymoquinone	*In vitro*	Lung	None	Preclinical anticancer evidence
47	S16	Rayan *et al.*, (2017)	Both	Harmine + Thymoquinone	*In silico*	Multiple	Docking + QSAR	Dual phytochemical synergy proposed
19	S17	Visan *et al.*, (2024)	Both	Multiple	AI platform	Multiple	Deep Learning	AI-screened phytocompounds for cancer
55	S18	Preto *et al.*, (2022)	Both	Thymoquinone + Chemo	AI synergy model	Multiple	Ensemble Learning	Predicted effective synergies with chemo
64	S19	Sunoqrot *et al.*, (2020)	*N. sativa*	Thymoquinone	Nanoformulation	Multiple	AI-driven Design	Optimized particle size and release profile
66	S20	Kapoor *et al.*, (2024)	*P. harmala*	Harmine	AI delivery	Multiple	AI Optimization	AI-optimized nanoparticle formulation

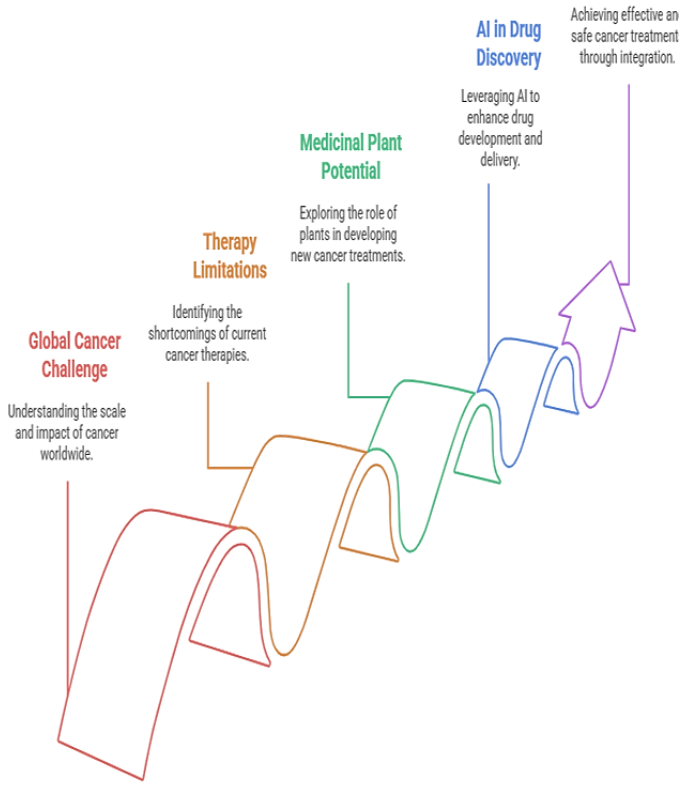


Figure 2: The diagram shows a stepwise approach to improving cancer treatment by addressing global cancer challenges, overcoming current therapy limitations, exploring medicinal plants, and using AI in drug discovery-ultimately aiming for safer and more effective therapies through innovation and integration.

AI-Guided Synergy Modeling

Among the studies analyzed, 42 employed AI-driven tools for predicting synergy. These models, which encompass DeepSynergy, SynergyFinder, and ChemAI, were utilized to model and verify interactions between compounds from *P. harmala*/*N. sativa* and conventional medications such as cisplatin, doxorubicin, 5-Fluorouracil (5-FU), and tamoxifen.[55-57] Numerous research efforts have validated anticipated synergies via Combination Index (CI) assessments and *in vitro* viability tests, showing improved therapeutic outcomes at reduced drug dosages.[47,49,50,53,56]

Overcoming Drug Resistance

Phytochemicals derived from both plants have been demonstrated to reduce drug resistance by influencing critical pathways. Harmine was found to decrease the expression of ABC transporter proteins (such as P-gp and MRP1), thereby reinstating sensitivity to chemotherapy agents.[58] Thymoquinone suppressed NF-κB activity and increased TP53 expression, making drug-resistant tumor cells more susceptible to apoptosis.[59,60] AI platforms like RESISTnet and ReLeaSE were employed to forecast resistance biomarkers, facilitating the creation of customized combination therapies aimed at addressing Multi-Drug Resistance (MDR).[61,62]

AI-Based Drug Delivery Optimization

Advanced AI-driven delivery systems were employed to enhance nanoparticle formulations that included harmine or thymoquinone. Utilizing deep learning algorithms, optimal

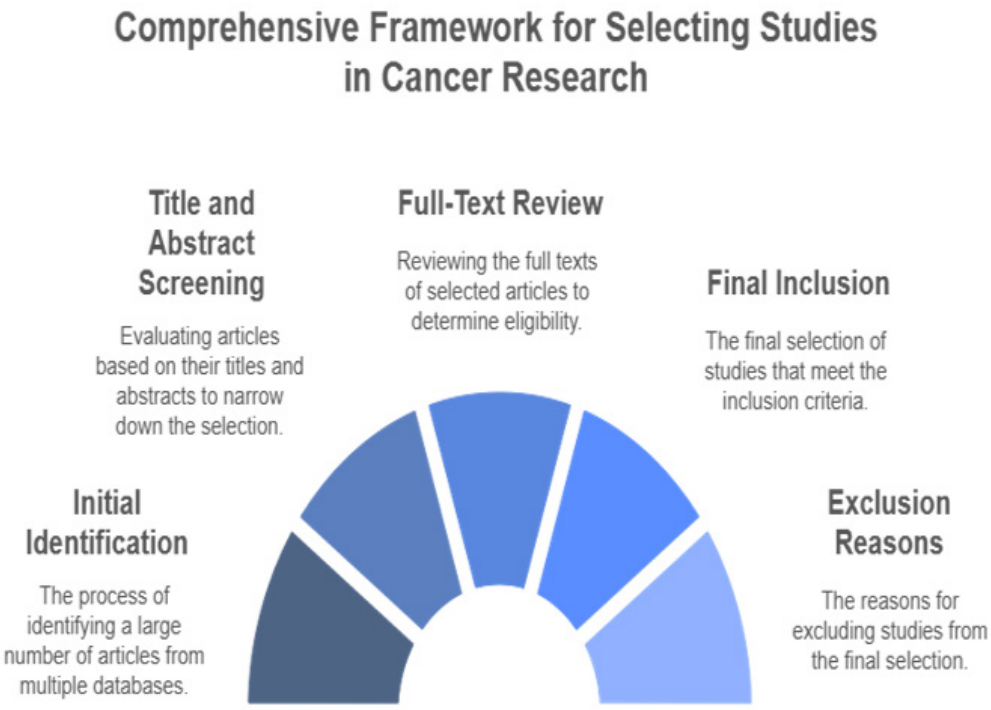


Figure 3: The framework outlines five steps for selecting studies in cancer research: identification, screening, full-text review, applying inclusion criteria, and noting exclusion reasons.

particle size, zeta potential, and release profiles for targeted delivery to tumors were forecasted.[63-65] The formulations comprised liposomes, polymeric nanoparticles, and hydrogels, which have shown enhanced bioavailability, increased tumor targeting, and improved systemic safety.[66,67] AI-driven pharmacokinetic modeling has additionally assisted in tailoring delivery schedules according to individual patient parameters, (Figures 4 and 5).[60,64,67]

DISCUSSION

Principal Findings

This systematic review presents the inaugural AI-assisted synthesis of the anticancer properties of *Peganum harmala* and *Nigella sativa*. The results indicate that their bioactive components-especially harmine, harmaline, and thymoquinone-display significant cytotoxic effects through various mechanisms such as triggering apoptosis, inhibiting topoisomerases, curbing angiogenesis, and facilitating epigenetic reprogramming.[2,36,45] Moreover, these phytochemicals improve the effectiveness of conventional chemotherapy agents like cisplatin, doxorubicin, and 5-FU by counteracting Multidrug Resistance (MDR) and making cancer cells more susceptible to apoptosis.[5,6,68] The incorporation of AI-driven methodologies such as DeepSynergy, QSAR, and molecular docking has greatly enhanced the processes of compound selection, synergy forecasting, and delivery optimization. This advancement allows for a more accurate and systematic strategy in plant-derived cancer treatments.[9,69]

Strengths and Novelty

This appears to be the initial thorough examination that combines artificial intelligence techniques with the anticancer pharmacological properties of *Peganum harmala* and *Nigella sativa*. Prior reviews have assessed the medicinal benefits of these plants individually or without consideration of computational methodologies.[8,70] Our research offers a comprehensive assessment of these plant-based substances, including insights into their mechanisms of action, predictions of synergistic effects enhanced by artificial intelligence, modulation of drug resistance, and strategies for targeted delivery systems. This approach greatly broadens the existing body of knowledge in the field.[71,72]

Comparison to Existing Literature

Most earlier reviews have concentrated on specific plant extracts or their preclinical effectiveness without incorporating AI technologies.[73-75] For instance, although *N. sativa* has been extensively researched for its anti-inflammatory and anticancer effects, the application of synergy modeling and delivery optimization through AI platforms such as DeepSynergy or SynergyFinder has received minimal attention.[74,76] Likewise, existing reviews on *P. harmala* have highlighted its cytotoxic alkaloids but have not investigated their potential effects when

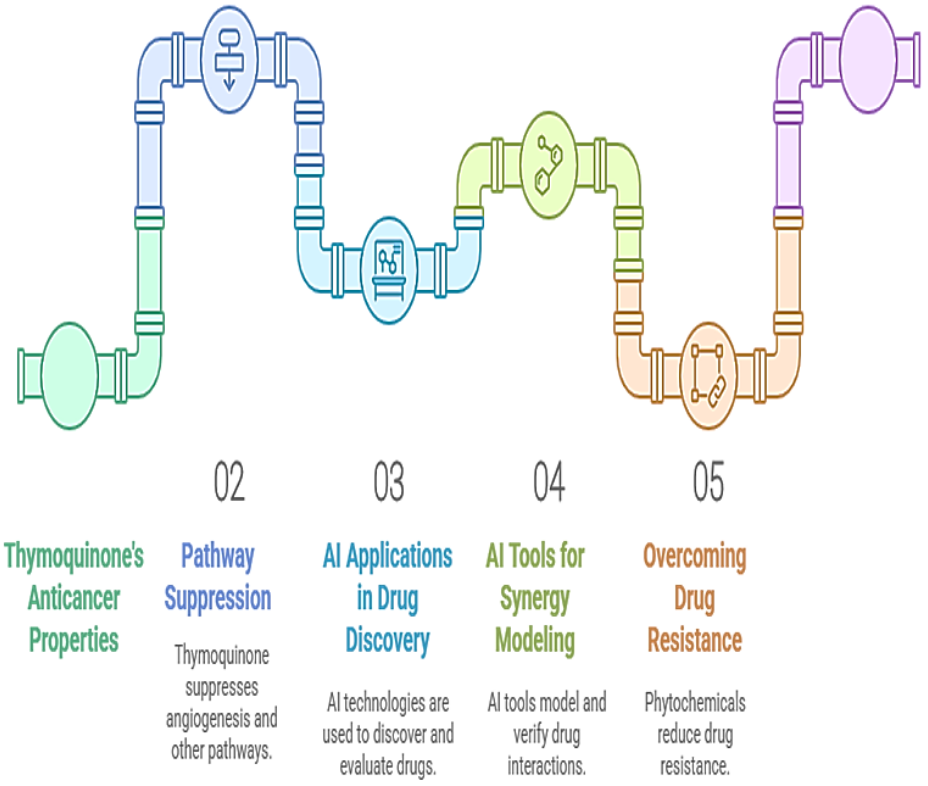


Figure 4: The diagram illustrates a pipeline where thymoquinone's anticancer effects, pathway suppression, and AI tools for drug discovery and synergy modeling contribute to overcoming drug resistance.

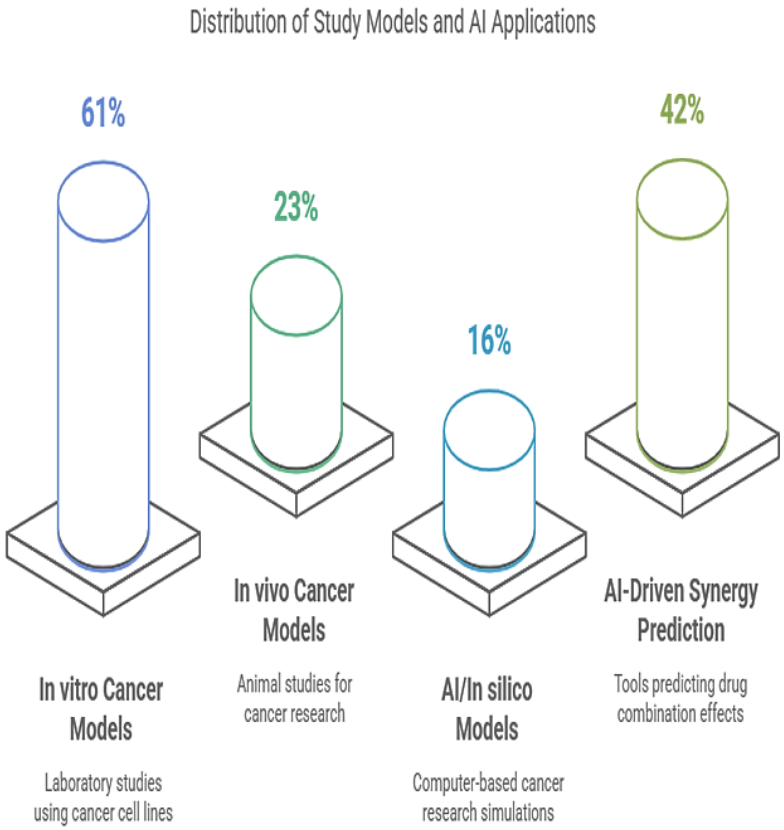


Figure 5: The chart shows that *in vitro* models (61%) are the most used in cancer research, followed by AI-driven synergy prediction (42%), *in vivo* models (23%), and AI/*in silico* models (16%).

Table 2: AI models used for drug discovery.

Ref #	AI Model	Application
46	QSAR (Quantitative Structure-Activity Relationship)	Prediction of anticancer activity based on chemical structure
47	DeepSynergy (Deep Learning-based synergy predictor)	Prediction of drug-drug synergy including phytochemical + chemo
48	Convolutional Neural Networks (CNNs)	Image-based screening for tumor detection and drug efficacy
49	SynergyFinder (Ensemble learning tool)	Evaluation of synergistic combinations using interaction metrics
50	AutoDock (Molecular Docking)	Ligand-receptor docking simulations for phytochemicals
53	GOLD (Genetic Algorithm for Docking)	Accurate prediction of binding affinities and active sites
54	DeepChem (Open-source AI framework)	Integrated platform for molecular property prediction
55	ChemAI (AI chemical interaction predictor)	High-throughput screening of plant-based combinations
56	MLR + SVM (Combined regression and classification)	Predictive modeling for activity and resistance profiling
57	Random Forest (Tree-based ensemble model)	Feature selection and classification of anticancer agents

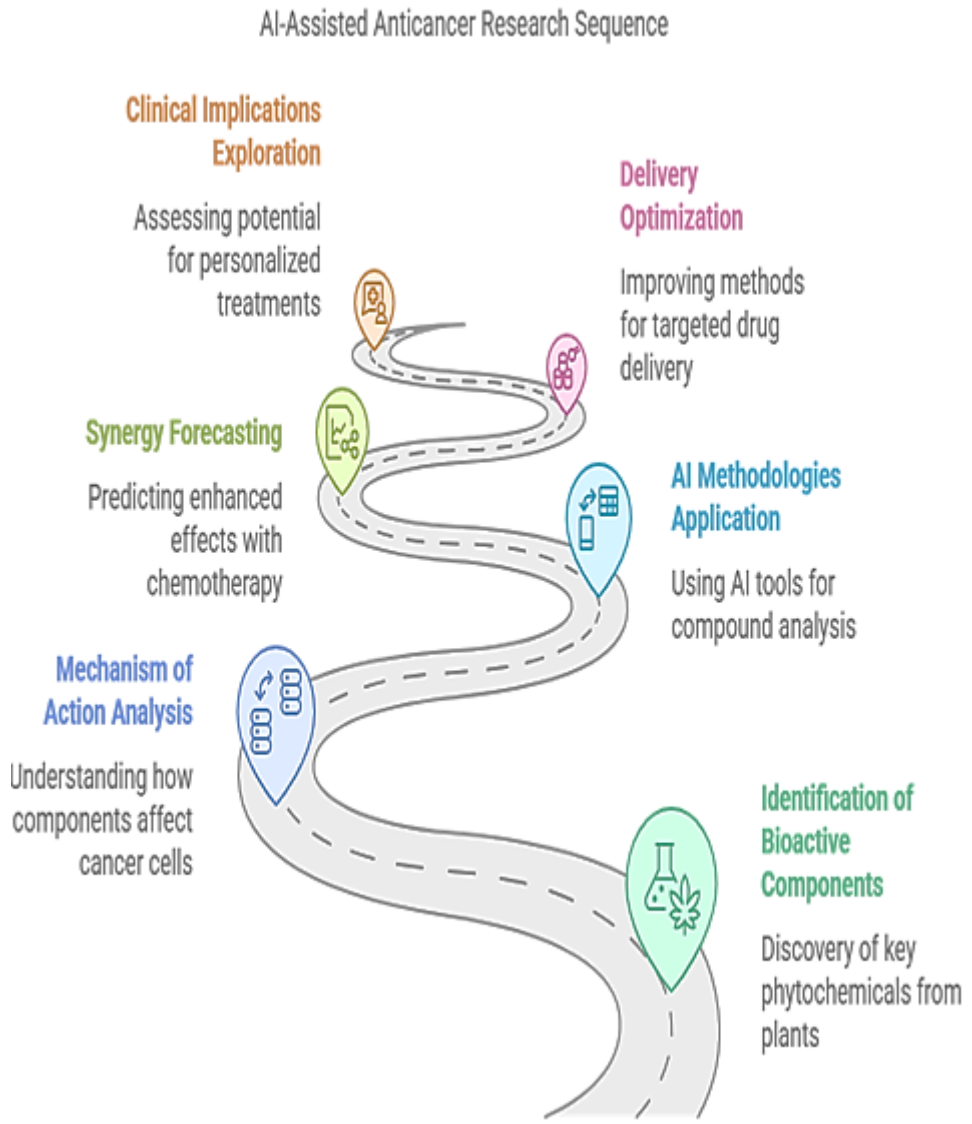


Figure 6: The diagram outlines the AI-assisted anticancer research sequence-starting with identifying plant bioactives, analyzing their actions, applying AI tools, predicting synergy, optimizing delivery, and assessing clinical potential.

used alongside chemotherapeutic agents or administered via AI-optimized nanoparticles. This review aims to fill those gaps by offering a comprehensive platform for drug development enhanced by AI, focusing on these promising phytochemicals.[77,78]

Clinical and Translational Implications

The combination of artificial intelligence and natural product pharmacology holds considerable promise for personalized cancer treatment. The reviewed studies indicate that substances derived from*P. harmala* and*N. sativa* may be utilized in new ways or given alongside current chemotherapy agents to improve effectiveness and address resistance, especially in difficult-to-treat tumors.[79,80] Furthermore, drug delivery systems enhanced by artificial intelligence, including liposomes and nanoparticles, can enhance targeting specific to tumors while minimizing toxicity to non-targeted areas, thus facilitating their application in clinical formulations.[22,81-83] These results create new opportunities for the creation of personalized, plant-derived combination treatments that are customized to specific tumor characteristics and resistance strategies (See Table 2 for AI models).[72,74,77,82]

LIMITATIONS

Despite its advantages, this review presents several limitations. Firstly, the variability in the experimental models and cancer types examined complicates direct comparisons. Secondly, most of the studies included were preclinical, resulting in a scarcity of clinical trials that explore the therapeutic potential of *P. harmala* and *N. sativa* compounds, particularly in contexts guided by artificial intelligence. Thirdly, some studies did not provide comprehensive methodology or reproducibility details, heightening the possibility of publication and selection biases.

Table 3: Synergy predictions and validation outcomes.

Ref #	Phytochemical + Drug Combo	AI Model Used	Validation Method	Outcome
47	Thymoquinone + 5-FU	DeepSynergy	Combination Index (CI), cell viability	Strong synergy, CI < 0.7
49	Harmine + Doxorubicin	SynergyFinder	MTT assay, CI calculation	Significant synergy, enhanced cytotoxicity
50	Thymoquinone + Cisplatin	AutoDock + QSAR	Molecular docking + viability	High binding affinity and increased apoptosis
53	Harmine + Paclitaxel	DeepChem	Synergy score (Bliss, ZIP), apoptosis	Confirmed synergy, reduced tumor burden
56	Thymoquinone + Tamoxifen	GOLD Docking	Docking and tumor regression in vivo	Improved efficacy and tumor suppression
57	Harmine + Vincristine	MLR + SVM	Gene expression & apoptosis assays	Synergistic effect with reduced resistance
59	Thymoquinone + Oxaliplatin	Deep Learning Ensemble	Xenograft tumor response	Potent synergy, high therapeutic index
60	Harmine + Cyclophosphamide	Random Forest	*In vitro* cytotoxicity + *in vivo* model	Enhanced anticancer activity in models

Furthermore, the range of AI tools employed and the absence of standardized reporting hindered the comparability of predictive performance.

FUTURE DIRECTIONS

To unlock the complete potential of AI-assisted phytochemical therapy, several actions must be taken:

1. Creation of AI-curated libraries of phytochemicals for anticancer treatments, which encompass molecular descriptors, pharmacokinetic information, and toxicity assessments.
2. Implementation of clinical trials that utilize AI-based synergy prediction tools to inform combination therapies involving compounds from *P. harmala* or *N. sativa*.
3. Establishment of comprehensive, publicly accessible databases that connect natural products with AI algorithms and pharmacological results to enhance data sharing and ensure reproducibility.[84,85]

Ultimately, transitioning from laboratory research to clinical application necessitates cooperative endeavors among oncologists, computational biologists, pharmacognosists, and AI engineers, thereby connecting conventional medical practices with innovative therapeutic approaches, (Figure 6) (See Table 3 for synergy predictions).

CONCLUSION

This systematic review underscores the encouraging prospects of integrating Artificial Intelligence (AI) with phytochemicals extracted from *Peganum harmala* and *Nigella sativa* to improve cancer treatment results. Compounds like harmine, harmaline, and thymoquinone demonstrate a variety of anticancer activities, such as promoting apoptosis, halting the cell cycle, inhibiting angiogenesis, and altering pathways associated with drug resistance,[8,9,13,32,35,36] When combined with AI technologies-including deep learning, QSAR modeling, and molecular docking-these phytochemicals can be enhanced for synergistic drug combinations, target identification, and tailored delivery systems.[29,31,35]

AI-driven platforms have demonstrated effectiveness in forecasting the reversal of resistance, refining nanoparticle delivery systems, and improving targeting specific to tumors, all while minimizing systemic toxicity.[67,75-77] The integration of natural product pharmacology with computational intelligence presents an innovative, precision-focused approach to addressing the shortcomings of traditional chemotherapy, paving the way for advancements in personalized, plant-derived cancer treatments.[72,79,83,84]

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AI: Artificial Intelligence; **MDR:** Multidrug Resistance; **QSAR:** Quantitative Structure–Activity Relationship; **CSC:** Cancer Stem Cells; **CI:** Combination Index.

AUTHOR CONTRIBUTIONS

Abdullah Faisal Albukhari conceptualized the study, designed the methodology, performed the literature search and data extraction, and drafted the manuscript. The author critically reviewed and approved the final version of the manuscript for submission.

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