Discovery Of Novel Anticancer Compounds From Peganum Harmala And Nigella Sativa In Cancer Therapy

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Abstract : Cancer remains one of the leading causes of death worldwide, demanding innovative therapeutic approaches. Natural phytochemicals offer multi-targeted and low-toxicity alternatives to conventional therapies. *Peganum harmala* (Syrian Rue) and *Nigella sativa* (Black Seed) are two medicinal plants rich in bioactive compounds such as harmine, harmaline, and thymoquinone (TQ), which exhibit potent anticancer, antioxidant, and Immunomodulatory effects. Artificial Intelligence (AI)-guided synergy mapping offers a systematic and data-driven method to predict synergistic interactions between phytochemicals and existing chemotherapeutic drugs. This article reviews the pharmacology, mechanisms of action, and advantages of *P. harmala* and *N. sativa*, and proposes an AI-guided workflow for identifying effective phytochemical–drug combinations in cancer therapy.

Keywords : Peganum harmala, Nigella saliva, harmine, thymoquinone, AI- Deep Synergy, Network pharmacology, Drug synergy, Cancer therapy.

1. Introduction

Cancer continues to be one of the most formidable global health challenges, characterized by uncontrolled cell growth, genetic instability, and resistance to apoptosis. Conventional treatment strategies such as chemotherapy, radiotherapy, and targeted therapy have significantly improved patient survival; however, they often lead to severe side effects, drug resistance, and reduced quality of life. These limitations have prompted researchers to explore natural and integrative treatment approaches that combine the efficacy of conventional medicine with the safety and biological diversity of herbal therapeutics.

In recent years, herbal-based therapeutics has gained increasing attention in oncology due to their ability to modulate multiple molecular targets simultaneously. Unlike single-target chemotherapeutic drugs, phytochemicals derived from medicinal plants exhibit pleiotropic actions that can regulate oxidative stress, apoptosis, cell cycle progression, and angiogenesis—key processes in tumor initiation and progression. Moreover, herbal compounds are generally less toxic, cost-effective, and accessible, making them suitable candidates for long-term adjunctive cancer therapy.(1)

Among the vast array of medicinal plants, Peganum harmala (Syrian Rue) and Nigella sativa (Black Seed) have emerged as potent sources of bioactive compounds with remarkable pharmacological potential. *P. harmala* is rich in β-carboline alkaloids such as harmine, harmaline, and harmalol, which demonstrate anticancer, antioxidant, and DNA-intercalating properties. These alkaloids have been shown to inhibit cell proliferation, induce apoptosis, and modulate key signalling pathways including PI3K/Akt, MAPK, and p53. On the other hand, *N. sativa* contains the Quinone compound thymoquinone (TQ), which exerts diverse anticancer effects by suppressing NF-κB activation, enhancing reactive oxygen species (ROS)-mediated apoptosis, and preventing angiogenesis in various cancer models.

Despite the growing evidence of their anticancer efficacy, the systematic exploration of phytochemical–drug synergies remains limited. The combinatorial complexity of natural compounds and chemotherapeutic agents presents significant experimental challenges, including time consumption, high costs, and limited reproducibility. To overcome these barriers, modern computational technologies such as Artificial Intelligence (AI) and Machine Learning (ML) have emerged as powerful tools in drug discovery and synergy prediction. These technologies enable the analysis of large-scale biological data, identification of synergistic interactions between phytochemicals and conventional drugs, and optimization of combination regimens before experimental validation. **(2)**

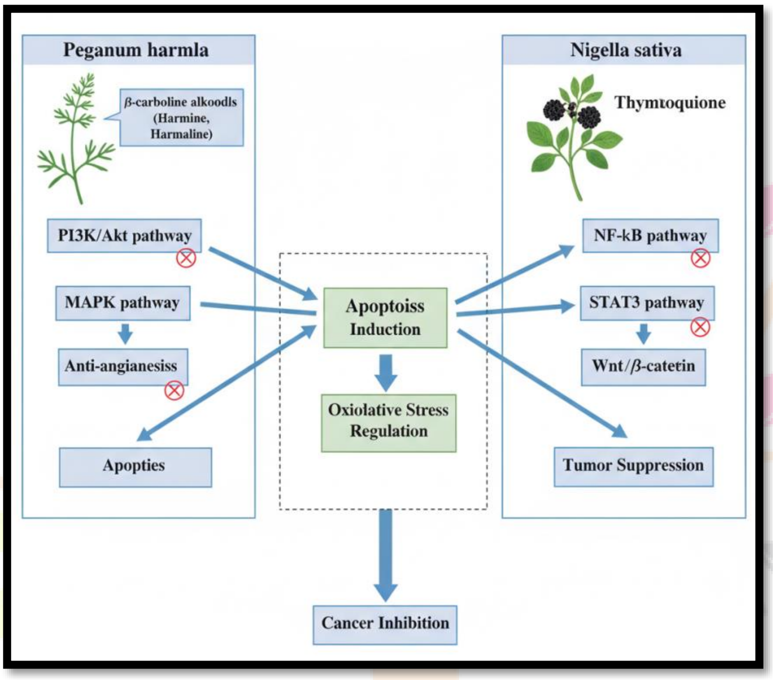

Figure 1 : Pharmacological Pathways of Peganum harmala and Nigella sativa.

Integrating AI-guided approaches with herbal pharmacology thus represents a transformative step toward computational phototherapy—an emerging discipline that bridges traditional medicine with data-driven innovation. By applying predictive algorithms, network pharmacology, and molecular docking techniques, researchers can accelerate the discovery of effective phytochemical–drug combinations tailored for specific cancer types.

2. Pharmacology Of Peganum Harmala And Nigella Sativa

The pharmacological significance of *Peganum harmala* (Syrian Rue) and *Nigella sativa* (Black Seed) has been recognized across ancient and modern medical systems for their diverse therapeutic applications. Both plants are rich in bioactive compounds exhibiting antioxidant, anti-inflammatory, antiproliferative, and anticancer properties. Their complex phytochemistry allows modulation of multiple cellular targets, making them valuable candidates in multimodal cancer therapy. The following subsections summarize their pharmacological profiles and relevance in oncology.(3)

2.1 Pharmacology of Peganum harmala (Syrian Rue)

2.1.1 Botanical and Phytochemical Overview

Peganum harmala, belonging to the family Zygophyllaceae, is a perennial herb native to the Middle East, Central Asia, and parts of India. Traditionally, it has been used as an antispasmodic, analgesic, and antimicrobial agent. The therapeutic potential of *P. harmala* primarily derives from its rich content of β-carboline alkaloids, including harmine, harmaline, harmalol, harman, and tetrahydroharmine. In addition, it contains quinazoline alkaloids such as vasicine and vasicinone, which contribute to its pharmacodynamics diversity.

These β-carbolines act as reversible inhibitors of monoamine oxidase (MAO-A and MAO-B), influencing neuropharmacological activity while exhibiting antiproliferative and pro-apoptotic effects in cancer cells. The alkaloids possess planar molecular structures that enable DNA intercalation, leading to inhibition of nucleic acid synthesis and tumor cell replication.

2.1.2 Pharmacological and Anticancer Activities

Extensive research has demonstrated that *P. harmala* exhibits cytotoxic and antiproliferative properties across multiple cancer cell lines, including breast (MCF-7), liver (HepG2), colon (HT-29), and lung (A549). The key mechanisms underlying its anticancer action include:

- **Cell Cycle Arrest:** Harmine and harmaline inhibit cyclin-dependent kinases (CDKs) and topoisomerase I, halting the transition of cancer cells at the G2/M phase.
- **Apoptosis Induction:** The alkaloids trigger mitochondrial-mediated apoptosis, characterized by caspase-3 activation, cytochrome c release, and downregulation of anti-apoptotic Bcl-2 proteins.
- **Oxidative Stress Modulation:** Through antioxidant enzyme regulation (SOD, catalase, and glutathione peroxidase), *P. harmala* mitigates reactive oxygen species (ROS)-induced DNA damage.
- **Angiogenesis Inhibition:** It suppresses VEGF (vascular endothelial growth factor) and related signaling cascades, impairing tumor vascularization.(4)

2.1.3 Molecular Targets and Signaling Pathways

At the molecular level, *P. harmala* modulates several key signaling pathways implicated in cancer progression:

- **PI3K/Akt/mTOR Pathway:** Inhibition of this pathway suppresses cell proliferation and enhances apoptosis.
- **MAPK/ERK Pathway:** Regulates mitogenic signaling and cell survival.
- **p53 Pathway:** Induces cell cycle arrest and apoptosis through DNA damage response mechanisms.

These multifaceted effects illustrate the plant's polypharmacological potential, making it a strong candidate for combination therapy in oncology.

2.1.4 Pharmacological Duality and Safety Profile

Interestingly, *P. harmala* exhibits **dose-dependent pharmacological duality**:

- **Low concentrations:** Act as antioxidants, neuroprotective, and cytoprotective agents.
- **High concentrations:** Induce cytotoxic, genotoxic, and pro-apoptotic effects.(6,19)

2.2 Pharmacology of Nigella sativa (Black Seed)

2.2.1 Botanical and Phytochemical Overview

Nigella sativa, commonly referred to as **Black Seed or Kalonji**, belongs to the **Ranunculaceae** family and is widely distributed in South and Southwest Asia, the Middle East, and parts of Europe. It has been extensively used in **Unani, Siddha, and Ayurvedic systems** as a therapeutic agent for respiratory, metabolic, and inflammatory disorders.

The pharmacological potency of *N. sativa* is attributed to its diverse phytochemical composition, including:

- **Thymoquinone (TQ)** — the principal bioactive constituent with strong anticancer and antioxidant activity.
- α-Hederin, nigellone, nigellidine, nigellicine, and fixed oils rich in linoleic and oleic acids.(5)

2.2.2 Pharmacological and Anticancer Activities

N. sativa exhibits a wide range of biological actions such as antioxidant, anti-inflammatory, immunomodulatory, hepatoprotective, and anticancer effects. Thymoquinone serves as the key anticancer molecule, acting through multiple mechanisms:

- **Apoptosis Induction**: Upregulates pro-apoptotic proteins (Bax, caspase-3, caspase-9) and downregulates anti-apoptotic Bcl-2 expression.
- **Cell Proliferation Inhibition:** Suppresses cellular growth factors and cyclins, preventing tumor expansion.
- **Oxidative Stress Regulation:** Increases the activity of antioxidant enzymes (SOD, CAT, GPx) and reduces malondialdehyde (MDA) levels, thereby maintaining redox homeostasis.
- **Anti-Angiogenic Effects:** Downregulates VEGF and MMP-9, limiting new blood vessel formation in tumors.
- **Chemo-sensitization:** Enhances sensitivity to drugs such as doxorubicin, cisplatin, and 5-fluorouracil, overcoming multidrug resistance (MDR) via modulation of P-glycoprotein and NF-κB pathways.

2.2.3 Molecular Targets and Pathways

Thymoquinone and other *N. sativa* constituents interact with several molecular pathways critical in tumorigenesis, including:

- **NF-κB and STAT3:** Downregulation leads to reduced inflammation and tumor survival signaling.

- **PI3K/Akt/mTOR:** Suppression enhances apoptosis and inhibits metastasis.
- **Wnt/β-catenin and MAPK:** Regulation of these pathways controls proliferation and migration of cancer cells.(6)

2.2.4 Pharmacokinetics and Drug Delivery Innovations

Despite its strong pharmacological profile, thymoquinone's bioavailability remains limited due to its poor solubility and rapid metabolism. To address this, modern research has developed nanocarrier-based formulations, such as:

- **TQ-loaded liposomes and nanoparticles**
- **Nanoemulsions and polymeric micelles**

Table 1 : Comparative Pharmacological Summary of Peganum harmala and Nigella sativa

Parameter	***Peganum harmala***	***Nigella sativa***
Major Phytochemicals	Harmine, Harmaline, Harmalol	Thymoquinone, α-Hederin, Nigellone
Principal Mechanisms	DNA intercalation, CDK inhibition, apoptosis	NF-κB inhibition, ROS modulation, chemo-sensitization
Key Pathways Affected	PI3K/Akt, MAPK, p53	NF-κB, STAT3, mTOR
Pharmacological Effects	Anti-proliferative, anti-antigenic	Pro-apoptotic, antioxidant, Immunomodulatory

3. Mechanism of Action of Peganum harmala and Nigella sativa in Cancer Therapy

3.1 Overview

The anticancer potential of *Peganum harmala* (Syrian Rue) and *Nigella sativa* (Black Seed) arises from their ability to modulate multiple molecular and cellular pathways involved in tumor initiation, progression, and metastasis. Both plants exert multitargeted effects—inhibiting cell proliferation, inducing apoptosis, regulating oxidative stress, and suppressing angiogenesis. The major bioactive compounds—β-carboline alkaloids (harmine, harmaline) from *P. harmala* and thymoquinone (TQ) from *N. sativa*—play central roles in these mechanisms. Their combined pharmacodynamics indicate potential synergistic efficacy when integrated into modern cancer therapy, especially with AI-guided mapping and predictive modelling.(7)

3.2 Mechanism of Action of Peganum harmala

1 Induction of Apoptosis

The β-carboline alkaloids of *P. harmala* activate **intrinsic (mitochondrial)** apoptotic pathways through multiple molecular events:

- **Mitochondrial Membrane Disruption:** Harmine increases the permeability of the mitochondrial membrane, facilitating the release of cytochrome c into the cytosol.

- **Caspase Activation:** The subsequent activation of caspase-9 and caspase-3 leads to programmed cell death.
- **Regulation of Bcl-2 Family Proteins:** *P. harmala* downregulates Bcl-2 (anti-apoptotic) and upregulates Bax and Bad (pro-apoptotic), tipping the balance toward apoptosis.(15)

2) Cell Cycle Arrest and DNA Interaction

- **Topoisomerase I and II Inhibition:** Harmine and harmaline inhibit these enzymes, leading to DNA strand breaks and suppression of replication.
- **CDK Inhibition:** Harmine blocks **CDK1 and CDK2**, arresting the cell cycle in the **G2/M phase** and halting mitosis.
- **DNA Intercalation:** The planar β-carboline ring allows intercalation into DNA, disrupting transcription and replication processes. These molecular interactions reduce uncontrolled proliferation in cancer cells.(8)

3) Oxidative Stress Regulation

At moderate concentrations, *P. harmala* exhibits **antioxidant activity** by scavenging free radicals and enhancing **SOD, catalase, and glutathione peroxidase** activity. However, at higher doses, it generates **ROS-mediated cytotoxicity**, inducing oxidative DNA damage in tumor cells—representing a **bimodal redox mechanism** beneficial in cancer control.(18)

4) Inhibition of Oncogenic Signaling Pathways

P. harmala exerts downstream inhibition of multiple oncogenic signaling cascades:

- **PI3K/Akt/mTOR pathway:** Suppresses proliferation and enhances apoptosis.
- **MAPK/ERK pathway:** Blocks mitogenic signaling and reduces metastatic potential.
- **p53 Activation:** Enhances DNA repair and apoptosis in damaged cells.
- **VEGF Pathway:** Inhibits tumor angiogenesis and nutrient supply.

5) Anti-Angiogenic and Anti-Metastatic Effects

Harmine reduces matrix metalloproteinase (MMP-2 and MMP-9) activity, which impairs extracellular matrix degradation and metastasis. It also downregulates VEGF and HIF-1α, suppressing new blood vessel formation crucial for tumor growth.

3.3 Mechanism of Action of Nigella sativa

1 Modulation of Apoptotic Pathways

Thymoquinone (TQ), the principal component of *N. sativa*, triggers apoptosis via both **intrinsic (mitochondrial)** and **extrinsic (death receptor)** mechanisms:

- **Intrinsic Pathway:** TQ enhances **ROS generation**, leading to **cytochrome c release** and activation of **caspase-9** and **caspase-3**.
- **Extrinsic Pathway:** TQ upregulates **Fas/FasL** and **TRAIL receptors**, stimulating **caspase-8** activation.

- **Mitochondrial Regulation:** TQ increases the **Bax/Bcl-2 ratio**, resulting in mitochondrial membrane potential loss and apoptotic signaling. (9)

2 Suppression of Cell Proliferation and Survival Signaling

TQ interferes with multiple oncogenic pathways:

- **NF-κB Pathway:** TQ inhibits phosphorylation and nuclear translocation of **NF-κB**, suppressing transcription of survival genes (Bcl-2, XIAP, and COX-2).
- **STAT3 Pathway:** Blocks **IL-6-mediated STAT3 activation**, reducing tumor growth and inflammation.
- **PI3K/Akt/mTOR Pathway:** Downregulates Akt phosphorylation, leading to decreased protein synthesis and increased apoptosis.
- **Wnt/β-catenin Pathway:** Inhibits β-catenin accumulation, reducing proliferation and invasiveness of tumor cells. These actions collectively restore normal cellular homeostasis and reduce tumor progression.

3 Anti-Oxidant and Redox Modulation

Thymoquinone acts as a **dual redox modulator**:

- **At low concentrations:** Scavenges ROS and enhances endogenous antioxidant defense.
- **At high concentrations:** Generates oxidative stress selectively in cancer cells, promoting apoptosis. This selective pro-oxidant action against tumor cells underpins its chemotherapeutic potential. (10)

4 Anti-Angiogenic and Anti-Metastatic Actions

TQ significantly downregulates **VEGF, MMP-2, MMP-9, and E-cadherin** dysregulation, preventing angiogenesis, tumor invasion, and metastasis. It also decreases expression of **CXCR4** and **integrins**, thereby impairing cancer cell migration and tissue colonization.(2)

5 Chemo-sensitization and Immunomodulation

TQ enhances the sensitivity of cancer cells to conventional drugs such as **doxorubicin**, **cisplatin**, and **5-fluorouracil** by:

- Inhibiting **drug efflux pumps (P-glycoprotein)**.
- Downregulating **NF-κB** and **Nrf2**, pathways associated with multidrug resistance.

Furthermore, TQ boosts innate and adaptive immunity by enhancing macrophage phagocytosis, T-cell activation, and cytokine (IL-2, IFN-γ) secretion, strengthening host anticancer defense.(11)

6 Comparative Mechanistic Insights

Mechanism	Peganum harmala (Harmine, Harmaline)	Nigella sativa (Thymoquinone)
Apoptosis	Mitochondrial pathway (caspase-3, Bax/Bcl-2 modulation)	Mitochondrial & death receptor pathways (caspase-8, -9, -3)
Cell Cycle Regulation	G2/M arrest via CDK and topoisomerase inhibition	G1/S arrest via β-catenin and PI3K/Akt inhibition
Oxidative Stress	Antioxidant at low dose; pro-oxidant at high dose	Redox duality: ROS scavenger and pro-apoptotic inducer
Angiogenesis	Downregulates VEGF, MMPs	Suppresses VEGF, HIF-1α, and integrins
Drug Synergy	Enhances chemotherapeutic cytotoxicity	Reverses multidrug resistance and increases chemo-sensitivity

7 Summary of Mechanistic Integration

Both *Peganum harmala* and *Nigella sativa* act through multi-targeted molecular mechanisms that regulate apoptosis, inhibit proliferation, and suppress tumor metastasis. Their complementary modes of action—harmine's DNA intercalation and kinase inhibition and thymoquinone's redox modulation and signal transduction control—suggest a synergistic therapeutic potential when used in combination.(9)

By integrating AI-guided synergy mapping, predictive algorithms can identify the most effective combinations of β-carboline alkaloids and thymoquinone with conventional anticancer drugs, optimizing efficacy while minimizing toxicity. This convergence of natural pharmacology and artificial intelligence paves the way for next-generation, personalized, and computationally optimized cancer therapeutics. (12)

4. AI-guided Synergy Mapping Workflow

The integration of **Artificial Intelligence (AI)** with **phytochemical synergy mapping** marks a transformative era in cancer pharmacology. However, to fully harness its potential, several advancements in data integration, computational infrastructure, and translational research are required. The following future directions outline the pathway toward achieving reliable and clinically applicable AI-guided phytochemical–drug therapies.(7)

4.1 Integration of Multi-Omics Data

Future research should focus on the integration of multi-omics datasets—including genomics, transcriptomics, proteomics, and metabolomics—to achieve a holistic understanding of how phytochemicals interact with cancer signaling networks. Multi-omics data can reveal patient-specific biomarkers and molecular signatures, enabling personalized phytochemical–drug mapping and improved prediction of therapeutic responses. Such integrative models can help bridge the gap between computational prediction and real-world biological complexity. (13)

4.2 Development of AI-Driven Databases

A critical step toward the advancement of computational phytotherapy is the establishment of AI-powered herbal–drug synergy databases. These curated repositories should compile chemical structures, bioactivities, target interactions, and validated synergistic outcomes from experimental studies. Open-access platforms would promote data sharing, reproducibility, and collaborative research across institutions, accelerating the pace of discovery in integrative oncology.

4.3 Clinical Translation and Validation

The **clinical translation** of AI-predicted phytochemical–drug combinations represents the ultimate goal of this research framework. Preclinical findings should progress to **phase I and II clinical trials**, focusing on evaluating pharmacokinetics, safety, and therapeutic efficacy in human subjects. Regulatory harmonization and interdisciplinary collaboration among pharmacologists, clinicians, and data scientists are essential to transform computational predictions into clinically viable treatment regimens.

4.4 Green AI and Quantum Simulation

Emerging technologies such as Green AI and quantum simulation are expected to redefine the computational landscape of drug discovery. Quantum computing can enable ultra-fast molecular docking and energy-state simulations, drastically reducing processing time and improving prediction accuracy. Meanwhile, Green AI approaches emphasize sustainable and energy-efficient computation, ensuring that large-scale modeling remains environmentally responsible and economically feasible.(14)

4.5 Standardization and Quality Control

The success of AI-guided phytochemical synergy research also depends on the standardization of experimental protocols. Uniform guidelines for phytochemical extraction, purification, structural characterization, and bioassay validation are crucial to ensure data reliability and reproducibility. Establishing international standards for herbal compound databases and bioinformatics pipelines will further enhance the credibility of AI-based predictions in pharmaceutical research.

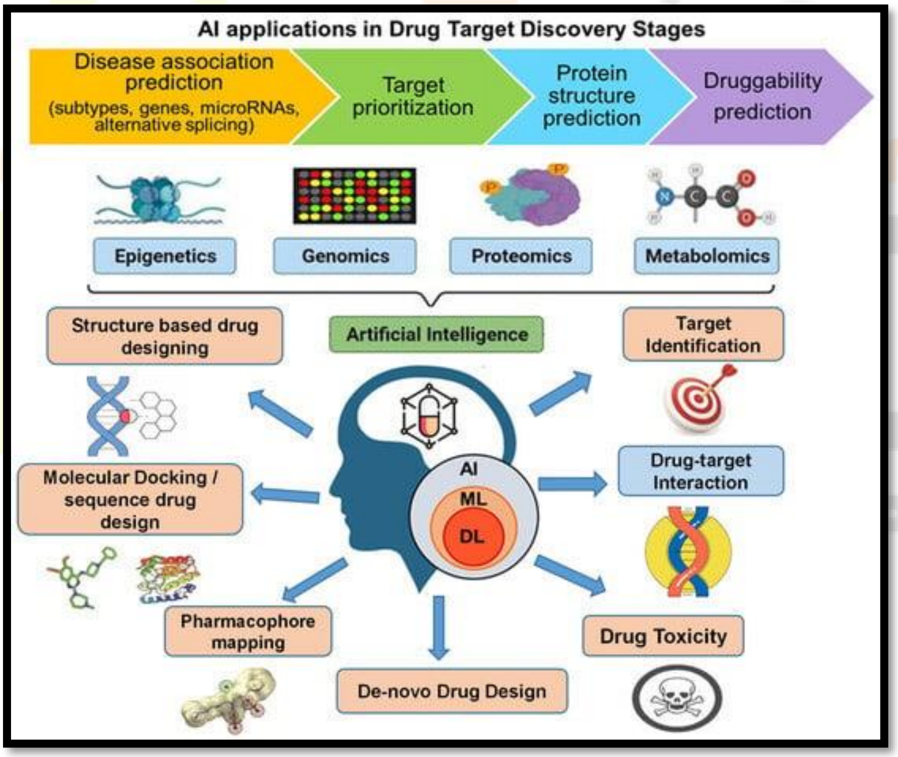

Figure 2 : Comprehensive integration of AI, omics, and ML in drug target discovery and design.

5. Advantages of AI-guided Phytochemical Synergy

The integration of Artificial Intelligence (AI) into phytochemical and drug synergy research represents a transformative advancement in oncology. AI-driven methods not only accelerate discovery but also enhance precision, reproducibility, and translational value. The following table summarizes the major advantages across key aspects of research and clinical development(15)

Table 2 : Advantages of AI-guided Phytochemical Synergy

Aspect	Advantage
Precision	AI algorithms efficiently screen and prioritize **the most promising synergistic phytochemical–drug pairs** from thousands of possible combinations by analyzing chemical fingerprints, biological targets, and molecular pathways.
Cost Efficiency	By reducing the dependency on high-throughput experimental assays, AI significantly **lowers research costs and shortens discovery timelines**, allowing only the most promising combinations to advance to laboratory validation.
Mechanistic Insight	AI enables **network-based pathway mapping** and **target overlap prediction**, providing mechanistic insights into how phytochemicals modulate cancer-related signaling cascades such as PI3K/Akt, NF-κB, and p53.
Personalized Medicine	AI models can be trained using patient-specific genomic and transcriptomic data, enabling **cancer-type or patient-specific synergy prediction**—a step toward **precision phytotherapy** and individualized treatment plans.
Safety Enhancement	AI-guided screening helps **predict potential herb–drug interactions, toxicological risks, and off-target effects** early in the development process, improving the overall safety profile of phytochemical-based therapeutic strategies.(16)

6. Potential Phytochemical–Drug Combinations

Artificial Intelligence (AI)-driven analyses and preclinical studies have highlighted several promising **phytochemical–drug combinations** that exhibit synergistic potential in cancer therapy.(17) Among these, compounds derived from *Nigella sativa* and *Peganum harmala* show notable interactions with conventional chemotherapeutic agents, enhancing efficacy while mitigating toxicity.

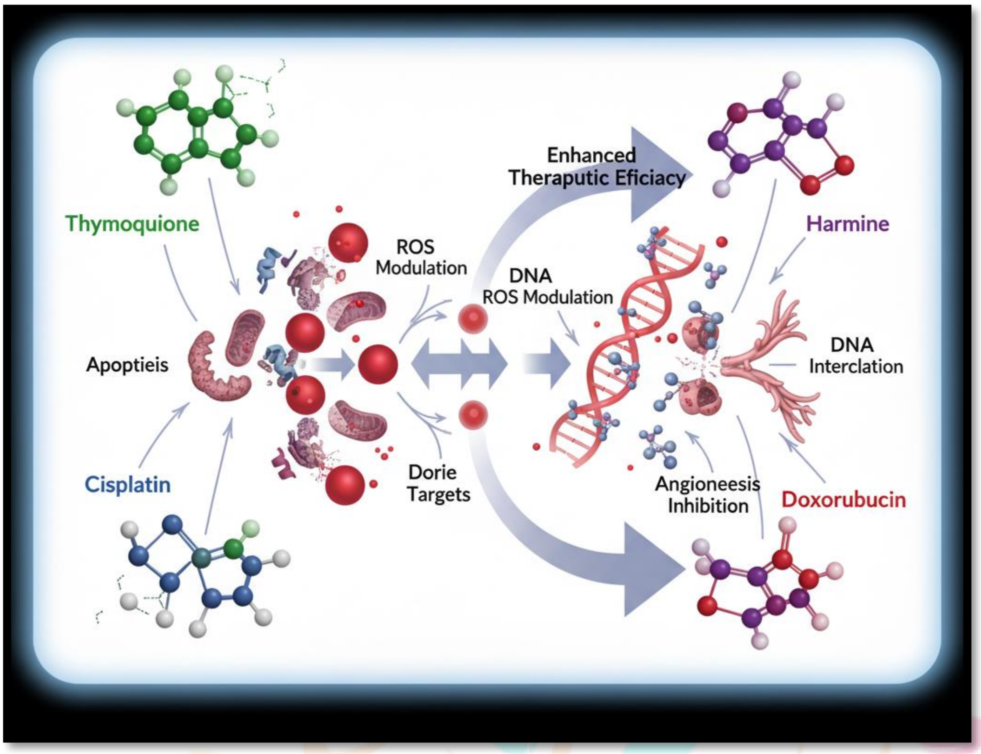

Figure 3 : Synergistic Mechanism of Phytochemical–Drug Combinations.

6.1 Thymoquinone and Cisplatin

The combination of thymoquinone (TQ), the principal bioactive component of *Nigella sativa*, with cisplatin has demonstrated remarkable synergistic effects in preclinical studies. This pairing enhances apoptotic activity in tumor cells and significantly reduces cisplatin-induced nephrotoxicity, a common dose-limiting side effect.(18)

6.2 Thymoquinone and Gemcitabine

Thymoquinone has also shown potential when combined with **gemcitabine**, a standard drug for pancreatic and breast cancers. Experimental findings suggest that TQ overcomes chemo resistance by down regulating NF-κB and PI3K/Akt signalling pathways while enhancing gemcitabine-induced apoptosis. In vitro validation supports this synergistic interaction, indicating that the combination may be beneficial in cancers characterized by drug resistance and poor prognosis.(19)

6.3 Harmine and Doxorubicin

The β-carboline alkaloid harmine, isolated from *Peganum harmala*, exhibits synergistic effects when paired with doxorubicin, a widely used anthracycline antibiotic. AI-guided predictive models suggest that harmine may inhibit angiogenesis and metastasis, thereby amplifying doxorubicin's antitumor potency while potentially reducing cardio toxic side effects.(5)

6.4 Harmaline and Paclitaxel

Similarly, harmaline, another key alkaloid from *P. harmala*, shows computationally predicted synergy with paclitaxel, a mitotic inhibitor used in various solid tumors. In silico simulations propose that harmaline enhances paclitaxel's anti-proliferative and pro-apoptotic effects through modulation of cell cycle regulators and microtubule-associated proteins. Although these findings are preliminary, they offer a promising foundation for future in vitro and in vivo validation studies.(20)

Table 3 : AI-Predicted Phytochemical–Drug Combinations and Validation Status

Phytochemical	Partner Drug	Predicted Synergistic Effect	Experimental Status
Thymoquinone	Cisplatin	Enhanced apoptosis, reduced nephrotoxicity	Preclinical confirmed
Thymoquinone	Gemcitabine	Overcomes drug resistance	In vitro validated
Harmine	Doxorubicin	Inhibits angiogenesis and metastasis	AI-predicted
Harmaline	Paclitaxel	Promotes apoptosis and	In-silico

7. Future Prospective

The integration of Artificial Intelligence (AI) with phytochemical synergy mapping marks a transformative era in cancer pharmacology. However, to fully harness its potential, several advancements in data integration, computational infrastructure, and translational research are required. The following future directions outline the pathway toward achieving reliable and clinically applicable AI-guided phytochemical–drug therapies.(21)

7. 1 Integration of Multi-Omics Data

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7.2 Development of AI-Driven Databases

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7. 3 Clinical Translation and Validation

The clinical translation of AI-predicted phytochemical–drug combinations represents the ultimate goal of this research framework. Preclinical findings should progress to phase I and II clinical trials, focusing on evaluating pharmacokinetics, safety, and therapeutic efficacy in human subjects. Regulatory harmonization and interdisciplinary collaboration among pharmacologists, clinicians, and data scientists are essential to transform computational predictions into clinically viable treatment regimens.

7.4 Green AI and Quantum Simulation

Emerging technologies such as Green AI and quantum simulation are expected to redefine the computational landscape of drug discovery. Quantum computing can enable ultra-fast molecular docking and energy-state simulations, drastically reducing processing time and improving prediction accuracy. Meanwhile, Green AI approaches emphasize sustainable and energy-efficient computation, ensuring that large-scale modeling remains environmentally responsible and economically feasible.(21)

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The success of AI-guided phytochemical synergy research also depends on the standardization of experimental protocols. Uniform guidelines for phytochemical extraction, purification, structural characterization, and bioassay validation are crucial to ensure data reliability and reproducibility. Establishing international standards for herbal compound databases and bioinformatics pipelines will further enhance the credibility of AI-based predictions in pharmaceutical research.(21,23)

8. Conclusion

The integration of AI-guided modeling and phytochemical pharmacology offers a novel framework for accelerating anticancer drug discovery. Peganum harmala and Nigella sativa represent potent natural sources whose bioactive compounds—harmine and thymoquinone—can synergize with conventional chemotherapy to enhance therapeutic efficacy and minimize toxicity.

Through AI-based synergy mapping, researchers can prioritize effective phytochemical–drug combinations, paving the way for personalized, integrative, and data-driven cancer therapies. Future studies should focus on standardization, large-scale validation, and clinical translation of these promising AI-assisted herbal formulations.

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