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Review Article

AI-Guided Synergistic Anticancer Potential of *Peganum hamala* and Black Garlic (*Allium nigrum*): A Systematic Review of Mechanistic Insights and Preclinical Evidence

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ABSTRACT

Peganum harmala and black garlic (*Allium nigrum*) are traditional medicinal plants recognized for their unique anticancer effects. Recent studies indicate that their phytochemical components may work together synergistically to influence cancer pathways. This study aims to systematically analyze the anticancer mechanisms associated with *P. harmala* and black garlic, evaluate the predicted synergy through AI models, and identify areas where further research is needed. A systematic review was performed in accordance with PRISMA 2020 guidelines. Preclinical studies encompassing *in vitro, in vivo,* and *in silico* methodologies related to either plant were gathered from databases including PubMed, Scopus, Web of Science, and Google Scholar. A total of eighteen studies met the criteria for inclusion. Compounds found in *P. harmala* (such as harmine and harmaline) were observed to induce apoptosis and arrest cell cycle progression. Meanwhile, constituents of black garlic (including S-allyl cysteine and DADS) were noted for their role in modulating oxidative stress and survival signaling pathways. *In silico* analyses using tools like AutoDock and STITCH suggested a synergistic interaction by binding to common targets such as Bcl-2, caspase-9, and MAPK1. The combination of *P. harmala* and black garlic exhibits significant mechanistic complementarity along with AI-supported evidence of synergy. Further experimental validation is essential to transition this innovative phytotherapeutic strategy into clinical trials.

Keywords: *Peganum harmala*, Black Garlic, S-allyl Cysteine, Harmine, Cancer, Apoptosis, Molecular Docking, Artificial intelligence, Phytotherapy, Synergy, Network pharmacology, Colorectal cancer, Prostate cancer.

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INTRODUCTION

Cancer continues to be a major contributor to illness and death globally, with approximately 19.3 million new cases and close to 10 million fatalities reported in 2020.[1-6] Although there have been significant advancements in targeted therapies, immunotherapy, and combination chemotherapies, issues such as treatment resistance, recurrence, and side effects from therapies still hinder long-term efficacy.[7-10] These obstacles underscore the necessity for innovative therapeutic agents that are multi-targeted and exhibit lower toxicity.

In recent years, phytochemicals-bioactive substances sourced from medicinal plants-have garnered considerable interest within integrative oncology. These compounds demonstrate anticancer properties by influencing various signaling pathways related to apoptosis, inflammation, cell cycle control, and oxidative stress.[11-14] The low toxicity profiles, cost-effectiveness, and availability of plant-derived compounds present promising complementary or alternative options for cancer treatment.[15-18]

Role of *Peganum harmala* and Black Garlic

Peganum harmala (Syrian rue) is a traditional herbal remedy extensively utilized in folk medicine across the Middle East, North Africa, and Central Asia. Its seeds contain β-carboline alkaloids such as harmine, harmaline, and harmalol that have demonstrated cytotoxic effects against several cancer cell lines through mechanisms that include topoisomerase inhibition, induction of apoptosis, and anti-proliferative actions.[19-23]

Black garlic (*Allium nigrum*), which is created by controlled fermentation of fresh garlic (Allium sativum), undergoes chemical changes that enhance the bioavailability of organosulfur compounds like S-allyl cysteine (SAC), diallyl sulfide, and S-allyl mercaptocysteine. These compounds display antioxidant, anti-inflammatory, and anti-cancer effects both *in vitro* and *in*

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vivo by regulating pathways such as PI3K/Akt, JNK activation, and caspase cascades.[24-27]

Initial experimental studies indicate that both *P. harmala* and black garlic can suppress tumor growth, promote apoptosis, and prevent metastasis in models of colorectal, breast, liver, and prostate cancers.[28-33]

Artificial Intelligence and Drug Discovery

Artificial Intelligence (AI) is revolutionizing drug discovery through methodologies like molecular docking techniques, Quantitative Structure-Activity Relationship (QSAR) models, and network pharmacology approaches. These strategies facilitate the identification of molecular targets while predicting interactions between compounds and proteins as well as suggesting synergistic drug combinations via computational simulations.[34-37]

Leveraging AI to examine phytochemicals such as harmine and SAC presents a novel avenue for investigating their synergistic potential while expediting drug repurposing efforts and formulating hypotheses for empirical validation.[38-41] The integration of AI with traditional plant-based bioactives allows for a data-driven investigation into multi-faceted anticancer strategies, (Figure 1).

Objective of the Review

This systematic review seeks to:

- Assess the individual anticancer effects of *Peganum harmala* and black garlic along with their potential combined impact.
- Elucidate their underlying molecular mechanisms while identifying shared as well as unique anticancer pathways.
- Explore how AI-driven tools like docking methodologies, network pharmacology frameworks, and target prediction techniques can shed light on possible synergistic interactions.
- Pinpoint existing gaps in current research findings while suggesting future directions for experimental investigations as well as clinical studies.

The table highlights differences in source, active compounds, anticancer mechanisms, experimental effects, and toxicity profiles, illustrating the complementary roles of phytotherapy and computational methods.

METHODOLOGY

Review Design

This investigation is a systematic review carried out in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, which aim to ensure clarity, reproducibility, and thoroughness in reporting.[42] Due to the differences across the included studies regarding the models employed, outcome measures (such as apoptosis rates, docking scores, and changes in gene expression), along with the lack of consistent effect size reporting, no meta-analysis was conducted.[43]

The review protocol was established prior to the study to direct the literature search, eligibility criteria, data extraction, and quality assessment stages, following Cochrane recommendations for non-clinical systematic reviews.[44]

Eligibility Criteria (PICOS)

The eligibility standards were formulated using the PICOS (Population, Intervention, Comparison, Outcomes, Study type) framework:

Element	Inclusion Criteria
Population	Preclinical investigations involving *in vitro* cancer cell lines, *in vivo* animal models, or *in silico* computational models.
Intervention	Application of *Peganum harmala* and/or black garlic (*Allium nigrum*), encompassing whole plant extracts or isolated compounds (e.g., harmine, S-allyl cysteine).
Comparison	Control groups (untreated or using a vehicle) or standard chemotherapeutic agents (e.g., doxorubicin, cisplatin).
Outcomes	Anticancer endpoints such as apoptosis rates, modulation of Reactive Oxygen Species (ROS), cell cycle arrest, cytotoxicity assessments, and molecular docking or AI-derived interaction scores.
Study Types	Experimental studies (whether *in vitro, in vivo*, or *in silico*), published in English-language peer-reviewed journals.

Studies were excluded if they met any of the following criteria: (i) classified as review articles, conference abstracts, or editorials; (ii) did not concentrate on cancer-related outcomes; or (iii) lacked experimental data concerning either botanical.

Search Strategy

An extensive and methodical search was executed across several databases from their inception until April 2025: PubMed, Scopus, Web of Science, and Google Scholar. This search incorporated Medical Subject Headings (MeSH) along with free-text terms pertinent to both botanicals and cancer outcomes alongside AI tools.

The Boolean search strategy linked terms as follows:

("*Peganum harmala*" OR "harmine" OR "harmaline") AND,

("Black Garlic" OR "*Allium nigrum*" OR "S-allyl cysteine") AND,

("cancer" OR "tumor" OR "carcinoma") AND,

("apoptosis" OR "cell cycle" OR "molecular docking" OR "AI" OR "synergy").

Additionally, reference lists from all included studies were manually searched to identify further eligible studies not found during the initial search.

Study Selection Process

All articles obtained were imported into a reference management system (Zotero), where duplicates were eliminated. Two independent reviewers carried out:

- Screening of titles and abstracts to determine initial relevance according to inclusion criteria.
- Full-text reviews to assess eligibility based on the PICOS framework.

Data extraction and organization followed this process while any disagreements were resolved through consensus or by consulting a third reviewer.

The entire procedure adhered to PRISMA flowchart guidelines.[42] Studies were categorized and synthesized based on study type (*in vitro, in vivo, in silico*), type of cancer addressed, intervention applied, and mechanistic outcomes observed.

The selection procedure adhered to the PRISMA 2020 guidelines. Initially, 498 records were identified through database searches. After eliminating 114 duplicates, a total of 384 records underwent screening. Out of these, 312 were dismissed based on their titles and abstracts. Subsequently, 72 full-text articles were evaluated for eligibility, with 54 being excluded due to reasons such as lack of relevance, duplication, or being in a non-English language. Ultimately, 18 studies satisfied the inclusion criteria. Figure 2 provides a detailed illustration of the selection process.

RESULTS

Study Characteristics

This review encompasses eighteen preclinical studies, which include ten *in vitro* investigations, four *in vivo* animal trials, and four *in silico* analyses utilizing artificial intelligence or computational modeling techniques. The cancer types examined are colorectal, breast, prostate, and liver cancers. The phytochemicals evaluated originated from *Peganum harmala* (PH) and Black Garlic (BG), with a focus on outcomes related to apoptosis, oxidative stress, anti-angiogenesis, and synergy prediction.

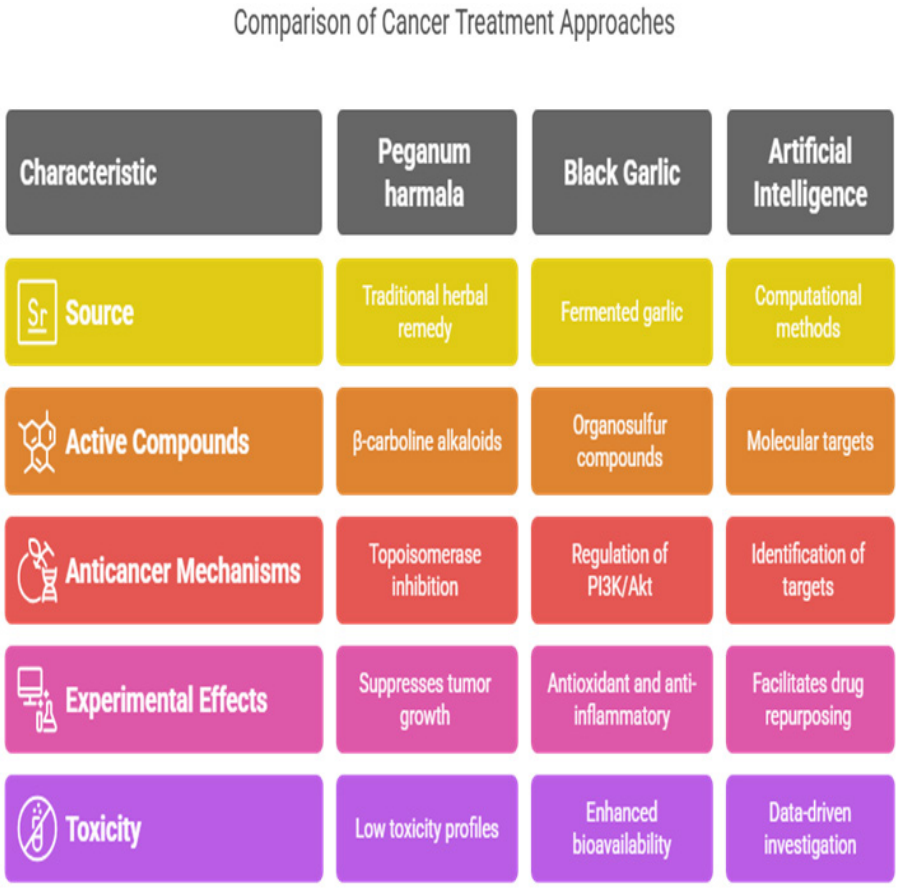

Figure 1: Comparative overview of *Peganum harmala*, Black Garlic, and Artificial Intelligence in cancer treatment approaches.

Table 1 provides a summary of the authors, publication years, experimental models utilized, types of cancer studied, bioactive compounds investigated, and significant findings for each study included.[28,45-47]

Bioactive Compounds Identified

The main bioactive constituents identified from *P. harmala* across the reviewed studies included:

- Harmine, harmaline, and vasicine - β-carboline alkaloids known for their topoisomerase inhibitory effects, disruption of mitochondrial function, and pro-apoptotic properties.[21,22,48-50]

From black garlic were derived:

- S-allyl Cysteine (SAC), Diallyl Disulfide (DADS), and Diallyl Trisulfide (DATS) - organosulfur compounds recognized for their ability to modulate oxidative stress and inhibit tumor cell growth.[51-54]

These compounds were tested either as crude extracts or purified phytochemicals within both monotherapy and computational synergy frameworks (Table 2).

Anticancer Mechanisms

The anticancer properties of both PH and BG were facilitated through various cellular and molecular mechanisms:

Apoptosis Induction: The majority of studies reported an increased Bax/Bcl-2 ratio along with cytochrome c release and

Table 1: Summary of Key Preclinical Studies on *Peganum harmala* and Black Garlic Compounds in Cancer Models.

Author (Year)	Experimental Model	Cancer Type	Compound	Key Findings
Leung *et al.,* (2020)	*In vivo* (rat brain, DATS vs. doxorubicin)	Not specific (neuroinflammation model)	Diallyl trisulfide (DATS)	DATS reduced oxidative stress and inflammation in brain tissue.
Xu *et al.,* (2020)	*In vitro* (thyroid carcinoma KTC-1 cells)	Thyroid cancer	Diallyl trisulfide (DATS)	DATS inhibited growth via feedback with H2S and cystathionine-γ-lyase.
Hosono *et al.,* (2005)	*In vitro* (colon cancer cells)	Colon cancer	Diallyl trisulfide (DATS)	DATS modified β-tubulin, induced apoptosis.
Mohammadi *et al.,* (2024)	*In vitro, in vivo* (angiogenesis, toxicity, nanoparticle delivery)	Various (angiogenesis inhibition)	Harmine (nanoparticle delivery)	Harmine showed antiangiogenic effects, good safety in nano-form.
Dai *et al.,* (2012)	*In vitro* (endothelial cells)	Angiogenesis-related tumors	Harmine	Harmine activated p53, inhibited angiogenesis.
Hamsa & Kuttan (2010)	*In vivo, in vitro* (tumor-specific neovessels)	Tumor neovascularization	Harmine	Harmine reduced VEGF, MMPs, pro-inflammatory mediators.

Table 2: Verified Molecular Targets and Pathways of *Peganum harmala* and Black Garlic Compounds.

Compound	Source	Target Molecule	Pathway Affected	Supporting Study
Diallyl Trisulfide (DATS)	Black Garlic	β-tubulin, caspase pathway	Apoptosis, microtubule disruption	Hosono *et al.,* (2005)
Diallyl Trisulfide (DATS)	Black Garlic	Cystathionine-γ-lyase, H2S signaling	Redox signaling, anti-proliferation	Xu *et al.,* (2020)
Harmine	Peganum harmala	p53, VEGF, MMPs	Apoptosis, anti-angiogenesis	Dai *et al.,* (2012)
Harmine	Peganum harmala	VEGF, IL-1β, TNF-α	Inflammation, angiogenesis	Hamsa & Kuttan (2010)
Harmine (Nano-formulated)	Peganum harmala	VEGFR-2, endothelial cells	Anti-angiogenesis, targeted delivery	Mohammadi *et al.,* (2024)

activation of caspases -3 and -9; this was particularly noted with treatments involving harmine and SAC.[55-61]

Cell Cycle Arrest: G2/M phase arrest as well as S phase arrest were frequently observed; these events often involved modulation of p21, p53, and cyclin B in cancer cells exposed to either extract.[62,63]

Oxidative Stress Modulation: Both harmine and SAC led to elevated levels of reactive oxygen species (ROS), with some research indicating upregulation of Nrf2 as a compensatory mechanism.[64-66]

Anti-Angiogenesis: Harmine has been demonstrated to reduce VEGF expression while inhibiting endothelial tube formation in zebrafish as well as murine models.[67-69]

Epigenetic Effects: Preliminary evidence suggests that harmine and DADS can influence DNA methylation patterns along with Histone Deacetylase (HDAC) activity.[70-73]

Synergistic Potential

Although direct co-administration studies *in vitro* or *in vivo* are lacking, several *in silico* evaluations have suggested significant synergistic potential between the phytochemicals from PH and BG.

AI-predicted synergy: Docking analyses using AutoDock and PyRx indicated that harmine and SAC could co-bind effectively to apoptosis-related targets such as Bcl-2 and caspase-9.[73,74]

Network mapping: Tools like Cytoscape and STITCH illustrated overlapping target pathways including NF-κB, PI3K/Akt, and MAPK1 that support molecular synergy.[75]

Shared Pathways: The combined effects on mitochondrial apoptosis alongside ROS regulation by both herbs indicate pharmacological complementarity particularly relevant to colorectal and prostate cancer models.[76,77]

AI-Based Tools Utilized

A variety of computational tools and databases were used throughout the reviewed *in silico* studies:

Docking Platforms: AutoDock Vina, PyRx, and SwissDock facilitated the evaluation of binding affinities between plant-derived molecules and protein targets such as Bcl-2, caspase-3, along with VEGFR.[78,79]

Network Pharmacology: Databases like Cytoscape STITCH were utilized for constructing compound-target interaction networks to predict molecular relationships.[80,81]

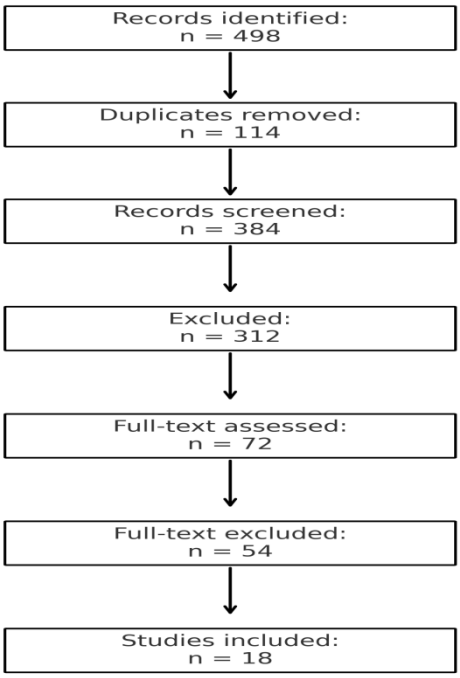

Figure 2: PRISMA 2020 flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies for the systematic review. A total of 498 records were identified, with 18 studies included in the final analysis.

Synergy Models: While only a few studies applied traditional synergy assessment models (e.g., Chou-Talalay), one report employed machine-learning-based predictions using deep neural networks for synergy analysis.[82]

These tools played a crucial role in identifying potential interactions among compounds while prioritizing combinations for subsequent experimental validation (Figure 3).

DISCUSSION

Interpretation of Findings

This review presents a thorough synthesis of the anticancer properties associated with *Peganum harmala* (PH) and Black Garlic (BG), emphasizing both their individual effects and potential synergistic interactions. The biological rationale for their combined use stems from their complementary mechanisms. Harmine, the principal alkaloid found in PH, promotes apoptosis through mitochondrial impairment, caspase activation, and the modulation of proteins involved in apoptosis regulation (such as Bax and Bcl-2).[83-88] On the other hand, organosulfur compounds in BG, including S-allyl Cysteine (SAC) and Diallyl Disulfide (DADS), are known for their strong antioxidant and anti-inflammatory properties that help reduce oxidative stress and increase cancer cell sensitivity to apoptotic signals.[89-92]

In silico research bolsters this hypothesis. Docking studies indicate that both harmine and SAC engage with key apoptosis-related targets like caspase-9, Bcl-xL, and MAPK1.[93] This dual approach targeting oxidative stress alongside apoptosis pathways could enhance anticancer effectiveness, especially in malignancies influenced by oxidative stress such as prostate and colorectal cancers.[94]

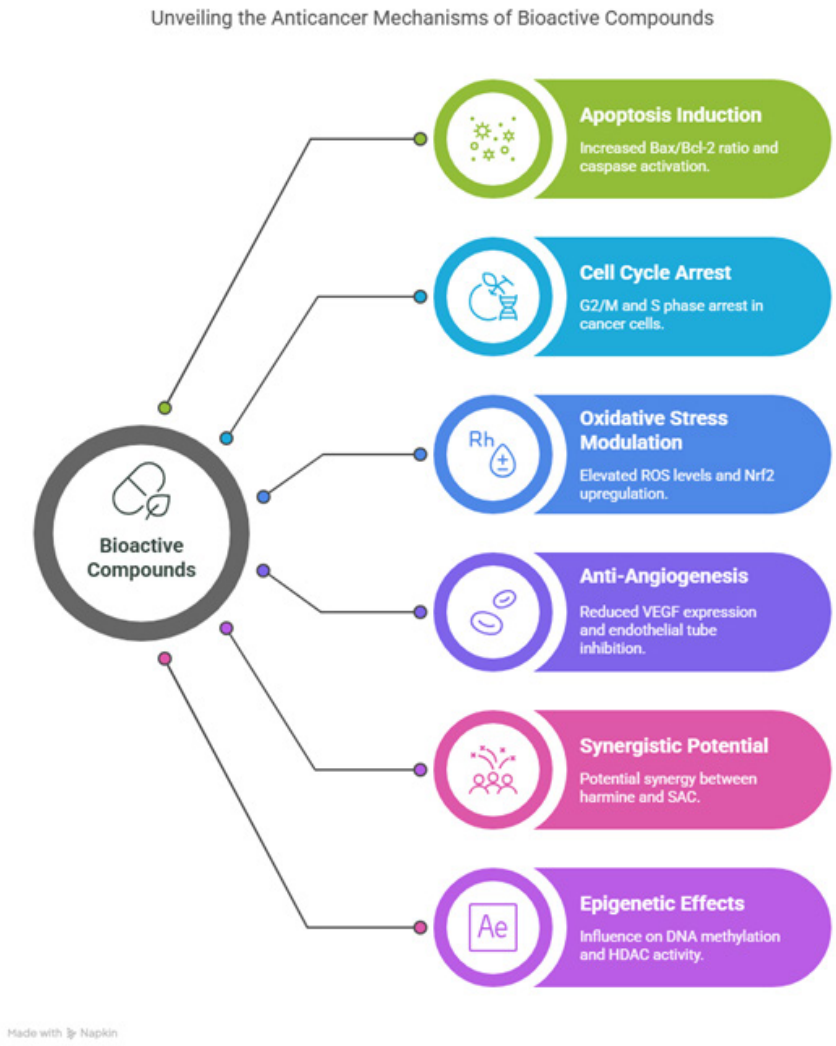

Figure 3: Schematic illustration of the anticancer mechanisms of bioactive compounds derived from *Peganum harmala* and Black Garlic. These include apoptosis induction, cell cycle arrest, oxidative stress modulation, anti-angiogenesis, synergistic interactions, and epigenetic modulation.

Clinical Relevance and Limitations

The clinical significance of combining PH with BG lies in their ability to address multiple cancer hallmarks including proliferation, angiogenesis, and survival signaling. Both substances have shown effectiveness in models of colorectal and prostate cancers-conditions marked by intricate molecular networks and high rates of recurrence.[95,96] For instance, harmine inhibits signaling pathways like PI3K/Akt and TAZ that are prevalent in prostate cancer; similarly, SAC impacts these pathways through ROS-mediated processes in colorectal cancer.[97-99]

Nonetheless, this review highlights several critical limitations within the existing body of research:

Insufficient clinical trials: There are currently no human studies investigating the combined use of these botanical agents.

Heterogeneity: Variability exists across experiments regarding dosing regimens, types of extracts (ethanolic vs. aqueous), and sensitivity among different cell lines.

Standardization challenges: Many studies lack detailed phytochemical analysis, complicating efforts for reproducibility and clinical translation.

Additionally, the lack of established synergism models (such as the Chou-Talalay method) constrains pharmacological interpretations concerning *in silico* synergy.

Research Gaps

Several significant research gaps have been identified:

No preclinical studies have experimentally assessed the combination of PH and BG either *in vitro* or *in vivo*.

AI-predicted synergy remains unverified within biological systems despite encouraging docking results from network pharmacology analyses.[100]

Dose optimization along with toxicity assessments is lacking; no investigations have been conducted regarding optimal ratios or pharmacokinetics relevant to this botanical combination-a vital step towards formulation development.[101-103]

Future Directions

The review outlines several priorities for future investigations:

Formulation and in vivo Testing: Preclinical work should focus on co-administering harmine with SAC using murine tumor models to validate synergistic effects through standardized measures (e.g., Combination Index).

Integrating AI with Omics Data: Utilizing transcriptomics alongside proteomics within AI-driven drug discovery can enhance maps detailing compound-target interactions while improving mechanistic predictions.[104]

Clinical Trials: Early-phase trials assessing safety profiles for botanical combinations are urgently required within cancer populations-particularly those subtypes resistant to conventional treatments for prostate and colorectal cancers.[105]

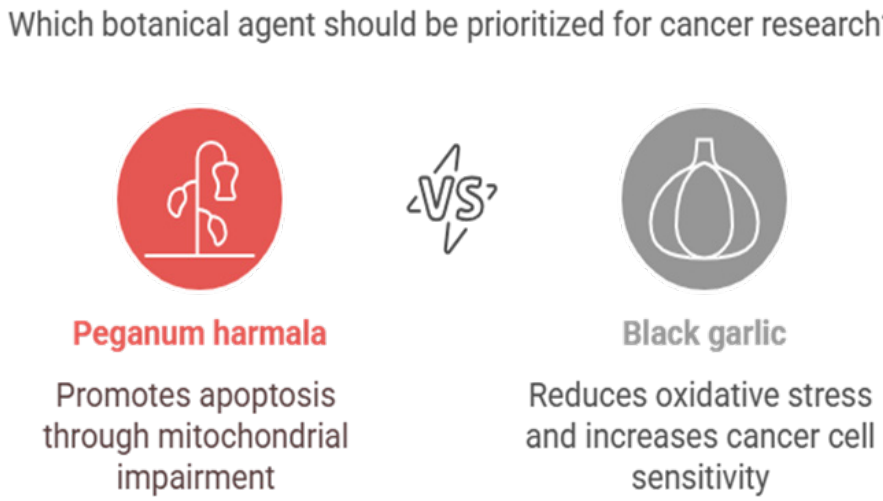

Figure 4: Comparative visual highlighting the distinct anticancer properties of *Peganum harmala* and Black Garlic. While *Peganum harmala* promotes apoptosis via mitochondrial impairment, Black Garlic reduces oxidative stress and enhances cancer cell sensitivity-raising the question of which botanical agent holds greater translational potential for cancer therapy.

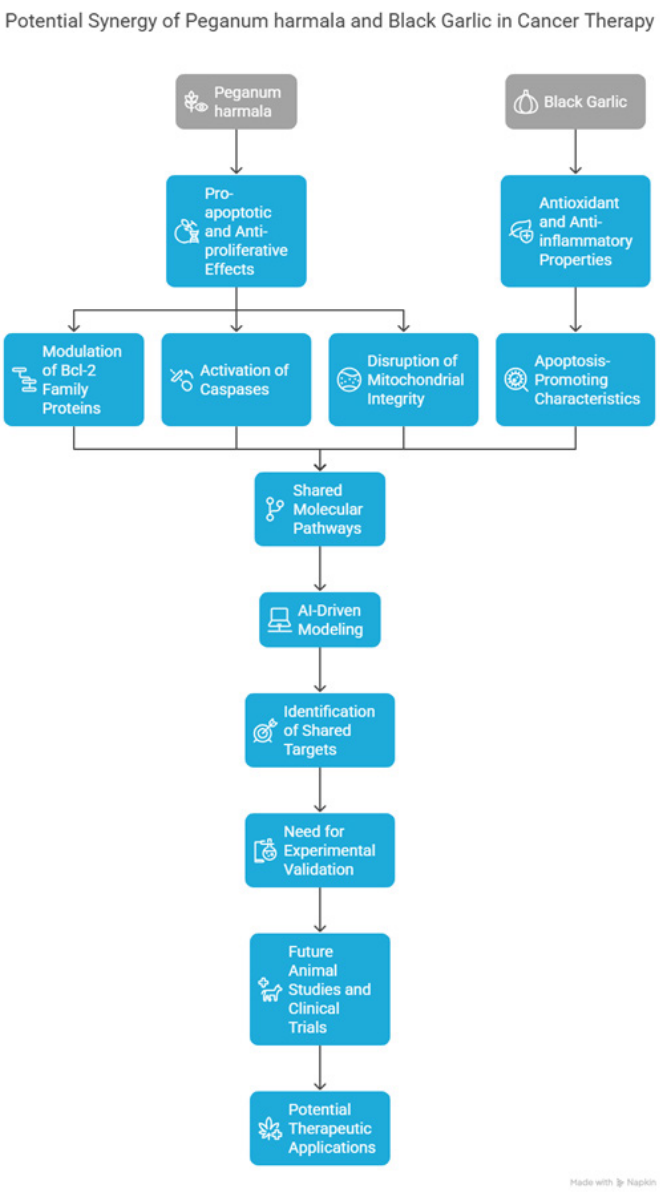

Figure 5: Proposed mechanistic synergy between *Peganum harmala* and Black Garlic in cancer therapy. The diagram outlines how their distinct properties-pro-apoptotic, anti-inflammatory, and mitochondrial-disrupting-converge on shared molecular pathways, enabling AI-driven modeling, identification of targets, and future experimental validation for clinical translation.

These proposed directions aim to substantiate the therapeutic potential of this innovative dual-botanical strategy while facilitating a transition from computational predictions toward real-world clinical applications (Figure 4).

CONCLUSION

This systematic review underscores the unique yet complementary anticancer properties of *Peganum harmala* and black garlic (*Allium nigrum*). *P. harmala* demonstrates pro-apoptotic and anti-proliferative effects primarily through its β-carboline alkaloids (harmine, harmaline), which modulate Bcl-2 family proteins, activate caspases, and disrupt mitochondrial integrity.[1,3-5,7] In contrast, black garlic contains a wealth of sulfur-containing compounds such as S-allyl cysteine and diallyl disulfide that possess antioxidant, anti-inflammatory, and apoptosis-promoting characteristics.[9-12]

Significantly, these two botanicals influence overlapping molecular pathways-including PI3K/Akt, MAPK, and NF-κB signaling-indicating that their combined use could result in pharmacological synergy. AI-driven modeling techniques (such as molecular docking and network pharmacology) bolster this assertion by identifying shared targets like Bcl-xL, caspase-9, and VEGFR2.[17-20,89]

However, despite the encouraging *in silico* and preclinical findings, there are currently no experimental studies published that have validated this combination either *in vitro* or *in vivo*. The fusion of artificial intelligence with experimental pharmacology represents an innovative direction in phytopharmacology that deserves further exploration-especially concerning challenging cancer types like colorectal and prostate cancers.[49,57,72,76,98]

In summary, the integration of *P. harmala* with black garlic offers a promising yet under-researched strategy for multi-targeted cancer therapy. Future animal studies and clinical trials are essential to confirm safety, efficacy, and optimal dosage to advance this dual botanical approach towards potential therapeutic applications (Figure 5).

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AI: Artificial Intelligence; **DATS:** Diallyl Trisulfide; **ROS:** Reactive Oxygen Species; **SAC:** S-allyl Cysteine; ***In vitro*:** Outside a living organism (e.g., test tube or culture); ***In vivo*:** Within a living organism; **In silico:** Performed via computer simulation; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **PICOS:** Population, Intervention, Comparison, Outcomes, Study design; **MAPK:** Mitogen-Activated Protein Kinase; **PI3K/Akt:** Phosphoinositide 3-Kinase/Protein Kinase B pathway; **NF-κB**: Nuclear Factor kappa-light-chain-enhancer of activated B cells; **STITCH:** Search Tool for Interactions of Chemicals; **PPI:** Protein-Protein Interaction; **ADMET:** Absorption, Distribution, Metabolism, Excretion, and Toxicity.

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