Pharmacognosy Reviews, 2025; 19(38):234-246.
www.phcogrev.com

Review Article

Soil Microorganisms in Cancer Therapy: AI-Driven Drug Discovery, Natural Compounds, and Strategies to Overcome Chemotherapy Resistance-Oil Microorganisms

Abdullah Faisal Albukhari*

Department of Medicine, Faculty of Medicine, King Abdulaziz University, Rabigh, SAUDI ARABIA.

ABSTRACT

The identification of new anticancer agents is essential for addressing chemotherapy resistance, a significant obstacle in cancer treatment. Soil microorganisms have proven to be a rich source of bioactive substances, and the integration of Artificial Intelligence (AI) is transforming drug discovery by streamlining screening and development processes. This systematic review examines the contributions of microbial metabolites from soil in cancer therapy, their mechanisms against chemotherapy resistance, and the role of AI in improving drug discovery. A systematic review of the literature was performed in accordance with PRISMA guidelines, utilizing databases such as PubMed, Scopus, and Web of Science. Included studies focused on anticancer compounds derived from microorganisms, their molecular actions, AI-facilitated drug discovery methods, and approaches to Mitigate Multidrug Resistance (MDR). Soil-derived microorganisms, particularly those from the genera *Streptomyces, Bacillus*, and Nocardiopsis, generate significant anticancer agents like doxorubicin, mitomycin C, and bleomycin. These agents demonstrate cytotoxicity through mechanisms such as inducing apoptosis, intercalating DNA, and inhibiting angiogenesis. Techniques driven by AI-such as deep learning and machine learning-have improved the detection of new microbial metabolites while facilitating predictions regarding drug interactions and enhancing chemotherapy effectiveness. Additionally, compounds from these microorganisms combat MDR by blocking efflux pumps, influencing apoptosis pathways, and disrupting DNA repair mechanisms. Utilizing soil microorganisms for the development of anticancer drugs alongside AI-enhanced screening represents a promising strategy to tackle chemotherapy resistance. Future investigations should prioritize metagenomic research, AI-guided genome exploration, and translational studies aimed at bringing microbial-derived compounds into clinical use. This interdisciplinary approach has great potential for creating next-generation cancer therapies that are more effective with minimized resistance.

Keywords: Soil Microorganisms, Anticancer Compounds, Artificial Intelligence, Drug Discovery, Chemotherapy Resistance, Multidrug Resistance, Microbial Metabolites, Oncology.

Correspondence:
Mr. Abdullah Faisal Albukhari
Department of Medicine, Faculty of Medicine, King Abdulaziz University, Rabigh-25732, SAUDI ARABIA.
Email: aabdulqaderalbukhari@stu.kau.edu.sa

Received: 09-05-2025;
Revised: 24-07-2025;
Accepted: 16-09-2025.

INTRODUCTION

Natural products are essential in cancer treatment, especially in addressing drug resistance, a major hurdle in chemotherapy. Compounds derived from microbes are also important for drug development, providing new potential treatment options. Nonetheless, the rising resistance to chemotherapy continues to pose a significant challenge in clinical settings.

DOI: 10.5530/phrev.20252349

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

Significance of Natural Products in Cancer Treatment

Chemopreventive and Therapeutic Agents

Natural substances and their derivatives play a crucial role in cancer treatment owing to their varied biochemical characteristics. These products can serve as chemopreventive agents and improve the effectiveness of current medications, aiding in the battle against drug resistance.[1-3] Sources and Diversity: Natural products originate from a range of sources such as plants, marine life, and microorganisms. These substances have played a crucial role in the advancement of anti-cancer medications that exhibit reduced side effects and enhanced therapeutic effectiveness.[4-6]

Role of Compounds Derived from Microorganisms in Drug Development

Microbial Metabolites

Compounds produced by microorganisms, including short-chain fatty acids and tryptophan derivatives, are crucial in regulating immune responses and boosting anti-tumor immunity. These metabolites have the potential to affect the results of chemotherapy and may aid in refining cancer treatment strategies.[1,7] Drug Discovery: Microorganisms serve as a vital source of natural compounds that exhibit anti-cancer properties, playing an important role in the development of novel pharmaceuticals.[4,5]

Emerging Resistance to Chemotherapy

Multidrug Resistance (MDR)

The issue of resistance to chemotherapy is widespread, as cancer cells frequently acquire the ability to withstand various medications. This phenomenon is a significant factor contributing to the ineffectiveness of chemotherapy and the associated mortality rates from cancer.[1-5] Strategies to Address Resistance: Natural compounds can affect various mechanisms of drug resistance by blocking drug-efflux proteins and modifying signaling pathways. They present encouraging approaches to counteract Multidrug Resistance (MDR) and enhance the results of chemotherapy.[8,9] The investigation of soil microorganisms as a potential avenue for cancer treatment presents a promising but relatively uncharted field. Moreover, the incorporation of artificial intelligence in drug development and the formulation of innovative approaches to tackle chemotherapy resistance are vital requirements in oncology.

METHODOLOGY

PRISMA Flow Diagram see (Figure 1)

Identification

Records identified from databases (PubMed, Scopus, Web of Science): 3500.

Records removed before screening (duplicates): 900.

Screening

Records screened: 2600.

Records excluded based on title and abstract: 1850.

Not relevant to soil microorganisms in cancer therapy (1100).

Did not discuss AI-driven drug discovery (500).

Non-original research or lacking methodology (250).

Eligibility

Full-text articles assessed for eligibility: 750.

Full-text articles excluded, with reasons:

Lacked data on chemotherapy resistance (250).

Did not include microbial-derived anticancer compounds (200).

No AI integration in drug discovery (150).

Included

Studies included in the systematic review: 150.

PRISMA Checklist (Table 1)

Search Strategy

The systematic review adhered to PRISMA guidelines with the following search strategy:

Databases searched: PubMed, Scopus, Web of Science.

Search terms used: "soil microorganisms AND cancer therapy", "AI-driven drug discovery AND microbial metabolites", "natural compounds AND chemotherapy resistance", "microbial-derived anticancer agents AND multidrug resistance."

Filters applied: Peer-reviewed articles, studies from 2000-2024, English-language publications.

Screening process: Titles and abstracts were reviewed, followed by full-text assessment for eligibility.

Risk of Bias Assessment

The Cochrane risk of bias tool was used to assess study quality.

Studies were evaluated for selection bias, performance bias, detection bias, attrition bias, and reporting bias.

High-quality studies were included in the synthesis.

Soil Microorganisms as Potential Cancer Treatment Agents

Soil-dwelling bacteria, including *Bacillus* spp. and *Nocardiopsis dassonvillei*, have exhibited encouraging prospects in cancer therapy. For instance, *Bacillus* spp. isolated from parks in New York City showed significant cytotoxic effects against lung cancer models, indicating their viability as therapeutic candidates.[10,11] *Nocardiopsis dassonvillei*, isolated from Egyptian soil, demonstrated notable anticancer effects on the MCF7 and HCT16 cell lines, underscoring the potential of soil microorganisms in the search for novel medicinal compounds.[12]

AI-Driven Drug Discovery

Artificial intelligence, especially machine learning, is transforming the process of discovering anticancer agents from natural sources, such as plants and microorganisms. AI methodologies enable thorough data analysis and predictive modeling, which are essential for uncovering new anticancer candidates. Nonetheless, there is a scarcity of systematic reviews that fully encompass these AI-based approaches.[7,9,12]

Overcoming Chemotherapy Resistance

The microbiome significantly impacts the effectiveness of chemotherapy, especially in cases of pancreatic cancer. The relationship between microbial components and chemotherapeutic agents can affect how these drugs are metabolized and how resistance develops. This indicates that interventions targeting the microbiome may improve the results of chemotherapy treatments.[13] Furthermore, cutting-edge approaches such as the integration of photodynamic therapy with chemotherapy have demonstrated enhanced effectiveness through their synergistic effects on treatment outcomes.[3,12,14] The incorporation of Artificial Intelligence (AI) in the evaluation and enhancement of bioactive compounds derived from soil, as well as in tackling chemotherapy resistance, represents a promising research frontier. AI has the potential to facilitate the identification and development of new compounds while refining treatment methodologies.

Role of AI in Screening and Optimization

AI in Compound Discovery

AI can be employed to analyze soil metagenomes for identifying novel bioactive substances. For example, sequence-tag-guided screening techniques applied to soil environmental DNA libraries have successfully led to the discovery of arimetamycin A, a powerful anthracycline that is effective against cancer cells resistant to multiple drugs.[15-17] Efficiency and Accuracy: AI models are capable of swiftly analyzing extensive datasets, allowing for the rapid identification of potential compounds that exhibit enhanced properties, surpassing the speed of conventional approaches.[16,17]

Mechanisms of Chemotherapy Resistance and Possible Solutions

Chemotherapy Resistance

One of the major obstacles in cancer therapy is chemotherapy resistance. This phenomenon frequently arises from cancer cells' capacity to circumvent the effects of drugs via multiple mechanisms, such as drug efflux, repair of DNA, and avoidance of apoptosis.[14] AI-Driven Solutions: Artificial intelligence can enhance the comprehension and prediction of resistance patterns through the analysis of intricate biological data, which may result in the creation of more effective treatment plans. Furthermore, AI's involvement in the early detection of cancer and in crafting personalized treatment approaches can help address resistance by customizing therapies to suit individual patient characteristics (Figure 2).[15,16]

Chemopreventive agents enhance the efficacy of medications and help mitigate resistance. Microbial metabolites play a role in modulating immune responses and strengthening anti-tumor immunity. Soil microorganisms, such as Bacillus spp. and *Nocardiopsis dassonvillei*, are integral to therapeutic approaches. AI technology facilitates drug discovery by utilizing data analysis and predictive modeling techniques. Addressing resistance entails inhibiting drug-efflux proteins and altering signaling pathways.

SOIL MICROORGANISMS AS A SOURCE OF ANTICANCER AGENTS

Soil microorganisms serve as a valuable reservoir of bioactive substances that have important uses in fields such as medicine, agriculture, and biotechnology. These substances are generated by diverse microorganisms, including bacteria and fungi, and are essential for microbial interactions and various environmental processes.[18] Types of Soil Microbes Generating Bioactive Compounds.

Bacteria

Streptomyces and Actinobacteria

These microorganisms are recognized for their capacity to generate a diverse array of antibiotics and various bioactive substances. They are significant producers of secondary metabolites, which play an essential role in microbial competition and communication within soil ecosystems.[18-21]

Bacillus Species

Strains of *Bacillus*, particularly *Bacillus* subtilis, are recognized for their ability to produce antibiotics effective against human pathogens like Methicillin-Resistant Staphylococcus Aureus (MRSA) and Candida albicans. Additionally, these bacteria play a significant role in nutrient recycling and the preservation of soil health.[22,23]

Other Bacterial Sources

Recent discoveries have revealed that new groups within the Actinobacteria, Chloroflexi, and the candidate phylum "Candidatus Dormibacteraeota" may serve as potential sources of bioactive compounds. These bacteria are frequently located in a variety of soil habitats and exhibit significant biosynthetic capabilities.[19,20]

Fungi

Penicillium and Aspergillus

These fungal species are recognized for their ability to generate bioactive phenolic compounds that exhibit antioxidant characteristics. They play a significant role in solid-state fermentation techniques aimed at extracting bioactive substances from agricultural waste, thereby supporting sustainable farming practices.[23]

Other Sources of Fungi

Fungi isolated from soil have demonstrated the ability to generate a range of bioactive substances, including compounds that possess antimicrobial and antioxidant properties. These substances

hold significant value for applications in both agriculture and medicine.[23,24]

Other Microbial Sources

Microbial Volatile Organic Compounds (mVOCs)

These substances are generated by a variety of soil microorganisms and contribute to the inhibition of plant pathogens. The generation and effectiveness of mVOCs are affected by both living organisms and environmental conditions in the soil, presenting opportunities for sustainable strategies to manage pathogens.[25]

Challenges and Future Directions

Isolation and Cultivation

One of the major obstacles in harnessing soil microbes for the production of bioactive compounds is the difficulty associated with isolating and cultivating most soil bacteria. However, progress in metagenomics and various molecular techniques is aiding in addressing these issues by enabling scientists to investigate the genetic capabilities of uncultured microorganisms.[20,21,23]

Sustainable Practices

Incorporating microbial bioactive compounds into sustainable farming methods represents a promising field of study. The use of beneficial microorganisms and microbes that promote plant growth can minimize reliance on chemical inputs while improving crop productivity.[24,25]

Antibiotic Resistance

Uncovering novel antimicrobial substances derived from soil microorganisms is vital for tackling the escalating problem of antibiotic resistance. Ongoing investigation into microbial diversity and the bioengineering of current compounds are crucial for creating new therapeutic solutions.[14,19,23,24]

Key Anticancer Compounds from Soil Microbes

Microorganisms, especially soil-based actinomycetes and fungi, have long been recognized as a valuable source of bioactive substances with noteworthy anticancer effects. The advent of drugs derived from these microbes has revolutionized cancer treatment by introducing highly effective chemotherapy options that operate through various mechanisms.

Past Success Stories

Numerous compounds sourced from soil have significantly impacted cancer therapy, showcasing strong effectiveness in clinical applications: Doxorubicin (*Streptomyces* peucetius) Doxorubicin is an anthracycline antibiotic obtained from *Streptomyces* peucetius and ranks among the most commonly prescribed chemotherapeutic agents. Its primary cytotoxic mechanism involves intercalating into DNA and inhibiting topoisomerase II, which results in double-strand breaks and apoptosis in rapidly proliferating cancer cells. This drug is extensively used for treating breast cancer, leukemia, lymphoma, and sarcomas.[26] Mitomycin C (*Streptomyces caespitosus*) Produced by *Streptomyces caespitosus*, mitomycin C serves as a DNA cross-linking agent that specifically targets hypoxic

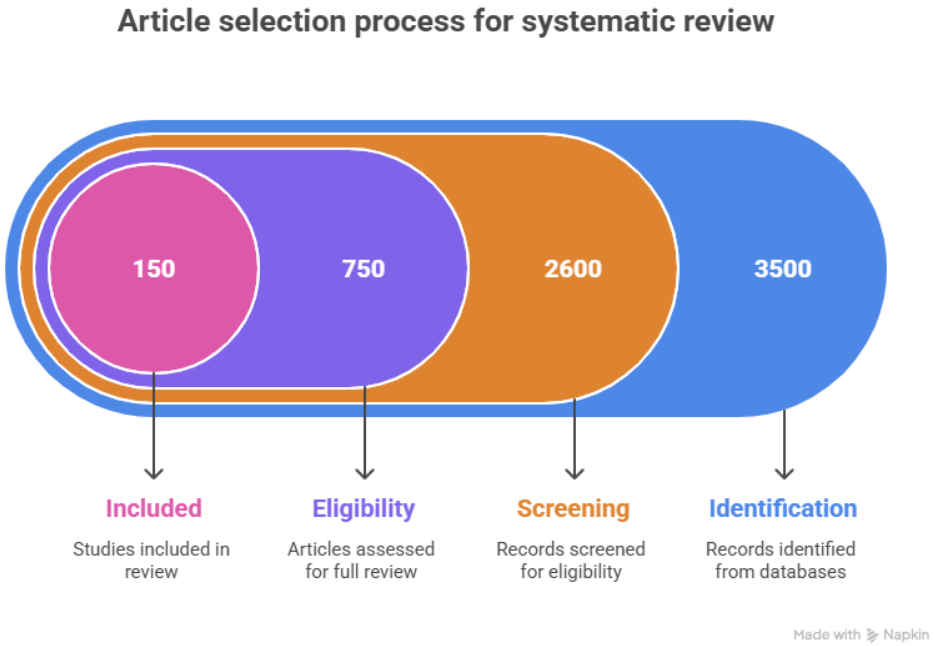

Figure 1: Prisma Flow Diagram for this research.

tumor cells. This alkylating compound disrupts DNA synthesis, proving effective against gastric, pancreatic, and bladder cancers. Furthermore, it has been utilized as an adjunctive treatment in radiation-sensitizing protocols due to its capacity to amplify oxidative damage within tumor cells.[27] Bleomycin (*Streptomyces verticillus*) Derived from *Streptomyces verticillus*, bleomycin causes both single- and double-strand DNA breaks through free radical generation, resulting in apoptosis. It finds considerable application in the treatment of Hodgkin's lymphoma, testicular cancer, and squamous cell carcinomas. Notably distinct from other chemotherapeutics, bleomycin exhibits minimal myelosuppressive effects, lowering the risk of bone marrow toxicity during combination chemotherapy.[28]

Newly Discovered Microbial-Derived Compounds with Anticancer Potential

While historical compounds have laid the groundwork for microbial metabolites in chemotherapy, ongoing research continues to enhance the arsenal of anticancer drugs. Innovations in metagenomics, genome mining techniques, and artificial intelligence-driven drug discovery have revealed new bioactive substances:

Lomaiviticin A and B (*Micromonospora* spp.)

These newly discovered agents induce DNA damage and show potential in targeting cancer stem cells-critical contributors to tumor recurrence and metastasis.[29]

Salinomycin (*Streptomyces albus*)

Initially identified as an antibiotic, salinomycin exhibits strong activity against cancer stem cells by selectively targeting tumor cells resistant to conventional chemotherapy.[30]

Plinabulin (*Aspergillus* sp.)

A microtubule-disrupting compound derived from fungal species that is currently undergoing clinical trials as an alternative to Vascular Endothelial Growth Factor (VEGF) inhibitors; it effectively diminishes tumor angiogenesis.[31]

Marinopyrrole A (*Streptomyces* spp.)

This natural pyrrolophene compound displays significant anti-leukemic properties by inhibiting NF-κB signaling-a pathway essential for cancer cell survival.

Mechanisms of Action of Soil Microbe-Derived Anticancer Agents

Anticancer compounds derived from microbes exert their effects through various mechanisms that often target critical characteristics associated with cancer:

Apoptosis Induction

Many microbial-derived agents initiate intrinsic or extrinsic apoptotic pathways leading to programmed cell death in malignant cells. Example: Doxorubicin activates p53-mediated apoptosis through DNA damage induction while salinomycin preferentially induces apoptosis in cancer stem cells.[32]

Cell Cycle Arrest

Certain soil-derived metabolites can disrupt cell cycle progression which inhibits tumor cell growth. Example: Mitomycin C and lomaiviticin A induce arrest at the G2/M phase thereby preventing successful mitosis in cancer cells.[33]

Table 1: PRISMA Checklist.

Section	Topic	Checklist Item	Status
Title	Title	Identify the report as a systematic review.	Yes
Abstract	Structured summary	Provide a structured abstract with background, methods, results, and conclusion.	Yes
Introduction	Rationale	Explain the rationale for the review.	Yes
Methods	Eligibility criteria	Specify inclusion and exclusion criteria.	Yes
	Information sources	Describe all databases searched (PubMed, Scopus, Web of Science).	Yes
	Search strategy	Provide a detailed search strategy.	Yes
	Study selection	Outline the process of selecting studies.	Yes
	Data collection process	Explain how data were extracted.	Yes
	Risk of bias	Address how bias was assessed.	Yes
Results	Study characteristics	Summarize the key characteristics of included studies.	Yes
	Synthesis of results	Provide a qualitative synthesis of findings.	Yes
Discussion	Summary of evidence	Summarize key findings and limitations.	Yes
Funding	Funding statement	Disclose any funding sources.	Yes

Inhibition of Metastasis

Compounds derived from microbes can inhibit migration and invasion of tumor cells by affecting epithelial-mesenchymal transition markers. Example: Marinopyrrole A blocks NF-κB signaling linked with processes involved in metastasis and invasion of cancerous cells.[34]

Targeting Angiogenesis

The formation of new blood vessels is crucial for tumor development; thus this process represents a vital therapeutic target. Example: Plinabulin disrupts microtubule dynamics leading to inhibition of VEGF levels thereby reducing tumor blood supply (Figure 3).[35]

AI-Powered Screening and Optimization of Soil-Derived Compounds

Traditional vs. AI-Based Drug Discovery

In the field of drug discovery, conventional approaches encounter various challenges, whereas Artificial Intelligence (AI) and Machine Learning (ML) present considerable benefits that can improve the overall process.

CHALLENGES OF CONVENTIONAL APPROACHES

Lengthy and Expensive

The traditional method of discovering drugs is often protracted and costly, typically requiring several years and substantial financial resources to transition a drug from its initial concept to market readiness.[36]

High Failure Rates

A significant number of prospective drugs do not succeed in the development phase because of unexpected problems, including toxicity or insufficient effectiveness, which are frequently discovered only in the later stages of the process.[36,37]

Limited Use of Data

Conventional approaches might not fully capitalize on the extensive data at hand, which could result in overlooking valuable insights that have the potential to enhance drug development.[31,36,37]

Advantages of AI and Machine Learning in Drug Discovery

Enhanced Efficiency and Accelerated Pace

Artificial Intelligence can greatly expedite the drug discovery process by automating intricate tasks and swiftly analyzing extensive datasets, thereby shortening the duration from initial discovery to market launch.[38]

Enhanced Precision

Machine learning algorithms are capable of accurately forecasting molecular characteristics and biological activities, facilitating the discovery of potential drug candidates.[39]

Data-Driven Insights

Artificial Intelligence facilitates the examination of complex, high-dimensional datasets, offering valuable insights that can inform decision-making processes and lower the likelihood of failures in pharmaceutical development.[36-38]

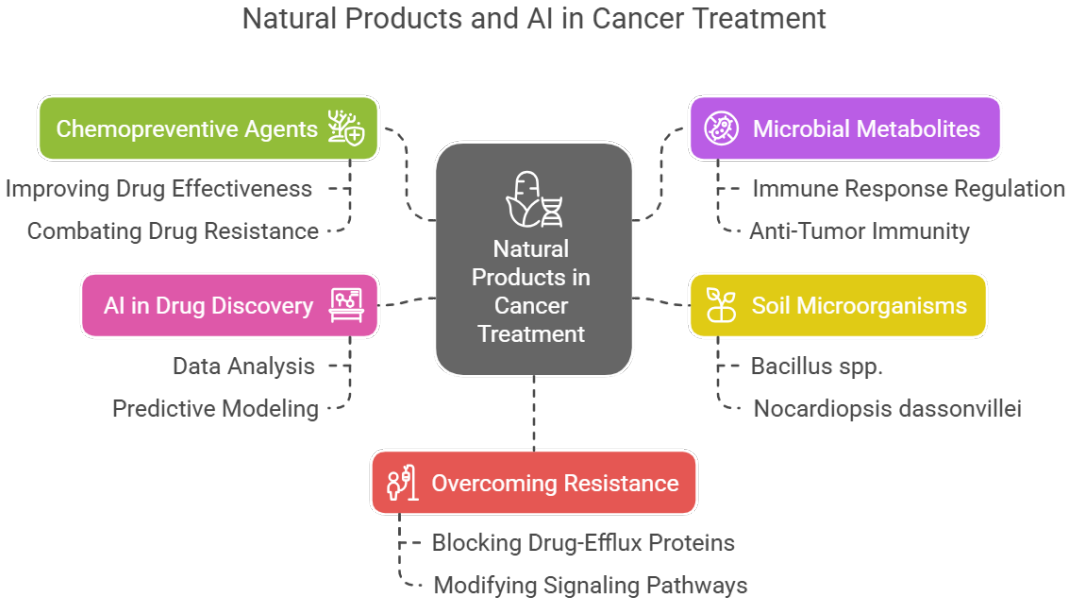

Figure 2: Natural products and artificial intelligence in oncology.

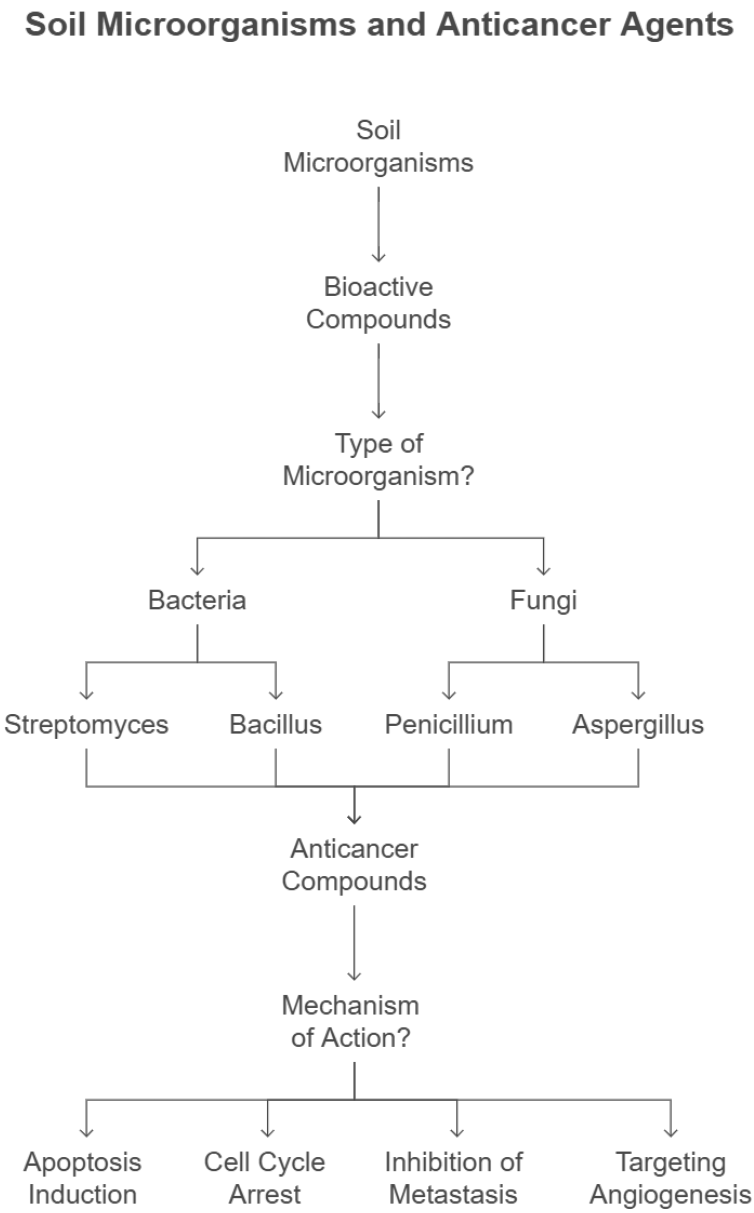

Figure 3: Soil microorganisms and cancer-fighting substances: Bioactive compounds produced by bacteria (such as *Streptomyces* and *Bacillus*) and fungi (including *Penicillium* and *Aspergillus*) generate anticancer agents that operate via mechanisms like inducing apoptosis, halting the cell cycle, preventing metastasis, and targeting angiogenesis.

Versatility at Different Phases

AI can be utilized throughout multiple phases of drug discovery, ranging from target validation to clinical trials, thereby improving the entire process.[31,38,39]

Innovative Strategies

Methods including deep learning, reinforcement learning, and graph neural networks provide novel avenues for modeling and forecasting drug interactions and characteristics.[31,36,39,40]

AI Techniques Used in Drug Screening

Artificial intelligence (AI) is progressively utilized in the field of drug discovery to improve both efficiency and precision. Its applications encompass genomic and metagenomic data analysis, optimization of compound structures through AI, as well as forecasting pharmacokinetics and toxicity levels. Below is a summary of the AI methodologies employed in these domains:

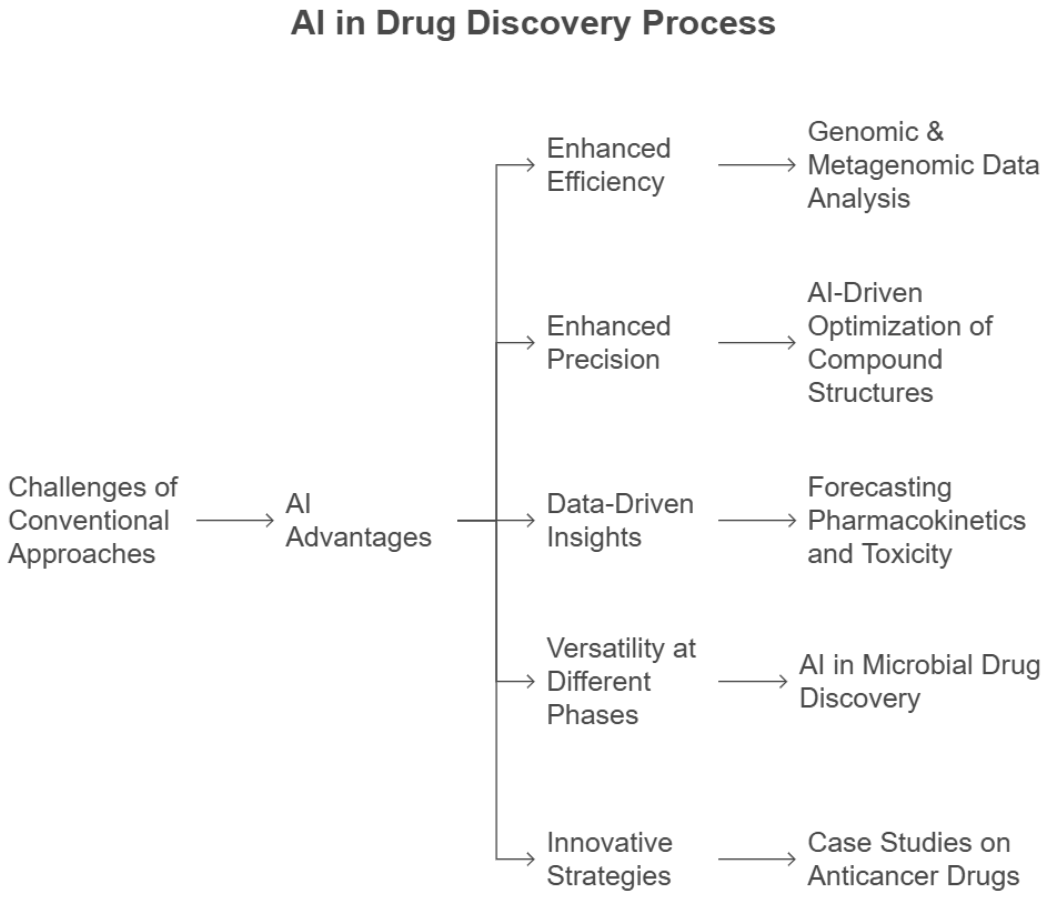

Figure 4: AI in the drug discovery process: By addressing traditional obstacles, AI boosts efficiency through the analysis of genomic and metagenomic data.

Genomic and Metagenomic Data Analysis

Machine Learning (ML) and Deep Learning (DL), both integral components of AI, play a vital role in uncovering new bioactive molecules from genomic information. These techniques facilitate the identification of antimicrobial peptides and various other compounds by effectively analyzing extensive datasets.[41-44]

AI-Driven Optimization of Compound Structures

Artificial intelligence plays a crucial role in virtual screening and computer-aided drug design for the enhancement of compound structures. Approaches like graph neural networks and structure-oriented methods are utilized to forecast molecular characteristics and interactions, aiding in the development of novel pharmaceuticals.[36,45]

Forecasting Pharmacokinetics and Toxicity

Artificial intelligence models are created to estimate drug toxicity and pharmacokinetics, thereby decreasing the chances of unsuccessful clinical trials. These models evaluate molecular characteristics and interactions to anticipate how a drug will act within the body.[36,44,46]

Examples of AI in Microbial Drug Discovery

The use of AI-enhanced microfluidics is transforming phenotypic drug discovery through the facilitation of swift screening of microbial compounds. This combination not only aids in discovering new drug candidates but also helps clarify biological pathways.[36,44-47]

Case Studies on AI-Driven Identification of Microbial-Derived Anticancer Drugs

AI methodologies have been utilized to uncover anticancer agents sourced from microbes. These approaches consist of examining extensive datasets to identify compounds that may exhibit anticancer characteristics, though specific case studies were not elaborated upon in the provided abstracts (Figure 4).[41,44-47]

It increases accuracy with AI-based compound optimization, offers insights for predicting pharmacokinetics and toxicity based on data, showcases adaptability in microbial drug discovery, and promotes novel strategies illustrated by case studies focused on anticancer medications.

Overcoming Chemotherapy Resistance with Soil-Derived Compounds

Chemotherapy resistance poses a major obstacle in the management of cancer, frequently resulting in unsuccessful treatment outcomes and subsequent cancer recurrence. This resistance arises from various mechanisms, including the activity of efflux pumps, modifications in apoptosis pathways, DNA repair processes, and the involvement of cancer stem cells.

Efflux Pumps

ABC Transporters and P-glycoprotein

Cancer cells frequently exhibit an overexpression of ATP-Binding Cassette (ABC) transporters like P-glycoprotein, which function to actively expel chemotherapeutic agents from within the cells, thereby diminishing their effectiveness.[48-51]

Altered Apoptosis Pathways

Bcl-2 and p53

The development of resistance may occur due to the excessive production of anti-apoptotic proteins, such as Bcl-2, alongside the reduced activity or mutations of pro-apoptotic factors like p53. These changes enable cancer cells to escape programmed cell death, facilitating their persistence even in the presence of chemotherapy.[52,53]

DNA Damage Repair Mechanisms

Improved DNA Repair

Cancer cells can boost their ability to repair DNA, enabling them to withstand the damaging effects of chemotherapy. This enhancement often involves the overactivation of DNA Damage Response (DDR) pathways, which are responsible for repairing DNA lesions caused by chemotherapy.[47-50]

Cancer Stem Cells

Role in Resistance

Cancer stem cells (CSCs) represent a specific group of tumor cells characterized by their ability to self-renew and their natural resistance to chemotherapy. These cells play a significant role in the resistance to treatment via various mechanisms, including the expulsion of drugs, improved DNA repair processes, and the avoidance of programmed cell death. CSCs are capable of adjusting to their surrounding tumor environment and frequently contribute to instances of cancer recurrence and metastasis.[45,47-53] The capacity of soil microorganisms to address drug resistance represents a significant field of study, especially through the application of Efflux Pump Inhibitors (EPIs) and agents aimed at resistant cancer stem cells. These methods seek to improve the effectiveness of chemotherapy and mitigate drug resistance.

Inhibitors of Efflux Pumps

Efflux pumps constitute a primary mechanism by which bacteria and cancer cells exhibit drug resistance. In bacterial organisms, common efflux pump types include those from the Major Facilitator Superfamily (MFS) and Resistance Nodulation and Division (RND) classes, whereas in cancer cells, ATP-Binding Cassette (ABC) transporters are frequently employed.[54-56] Inhibiting these pumps has the potential to make resistant strains more susceptible to medications, as demonstrated in antifungal resistance, where the use of efflux pump inhibitors can improve the effectiveness of azole drugs.[53-55] Phyto-therapeutics, which originate from plants, demonstrate promise as effective agents in addressing antimicrobial resistance by reversing bacterial drug resistance.[54,56]

Compounds Targeting Resistant Cancer Stem Cells

The abstracts presented do not specifically focus on compounds that target resistant cancer stem cells; however, by inhibiting efflux pumps in cancer cells, there is an indirect mechanism at play that can improve the effectiveness of chemotherapy drugs against these cells.[52]

Enhancers of Chemotherapy Effectiveness

The effectiveness of treatment can be enhanced by the combination of EPIs with antibiotics or chemotherapeutic drugs, particularly in combating resistant microorganisms and cancer cells.[57] This approach is promising but requires further research to develop potent inhibitors with low toxicity.[48,51,54,55]

Case Studies and Examples

Soil microbiomes serve as repositories for resistance genes, and soils contaminated with metals can promote the development of antibiotic resistance via efflux pumps. This underscores the possibility of employing either natural or synthetic Efflux Pump Inhibitors (EPIs) to reinstate the effectiveness of antibiotics.[56] The application of heterologous expression systems for the identification of inhibitors targeting fungal efflux pumps represents an effective strategy for the discovery of novel Efflux Pump Inhibitors (EPIs).[52,54]

Challenges and Prospective Paths in Cancer Treatments from Soil Microbes

The identification of anticancer agents sourced from soil microorganisms has resulted in significant progress in the field of chemotherapy. Nonetheless, numerous obstacles remain in converting these findings into effective clinical applications. These challenges encompass intricate biosynthetic processes and constraints related to AI-based drug discovery. By tackling these

concerns through innovative research approaches, it is possible to improve the effectiveness, scalability, and clinical outcomes of cancer therapies derived from microbes.[54,55]

Challenges in Natural Drug Discovery from Soil Microbes

Complexity of Microbial Biosynthesis

The process by which microbes synthesize anticancer compounds is frequently intricate and not well comprehended. Numerous soil microorganisms generate bioactive metabolites via complex enzymatic pathways, which are controlled by genetic clusters that often remain dormant or hidden in laboratory settings.[58,59] To address this challenge, it is essential to employ metagenomic strategies, utilize genetic engineering techniques, and implement AI-driven genome exploration to enhance and streamline biosynthetic pathways for the large-scale manufacture of pharmaceuticals.[59]

Increasing Production of Microbial-Derived Compounds for Clinical Applications

Despite the identification of promising anticancer agents, the challenge of scaling their production for clinical trials and commercial drug manufacturing persists. Numerous bioactive microbial metabolites are generated in limited quantities, complicating the processes of industrial fermentation and bioprocessing.[55,57-59] Additionally, differences in the conditions for microbial growth can influence the consistency of compounds, necessitating the refinement of fermentation methods, synthetic biology strategies, and metabolic engineering to enhance yield and stability.[56,58,59]

Challenges in AI-Driven Drug Discovery

Data Constraints in AI Evaluation of Natural Products

The effectiveness of AI-driven drug discovery is significantly dependent on extensive, high-quality datasets to train machine learning algorithms. Nonetheless, libraries of natural products are often restricted, lacking completeness and being skewed towards compounds that are well-studied. This limitation hampers the capability of AI to discover innovative drugs derived from microbial sources.[60,61] Additionally, microbial genome databases that are accessible to the public frequently suffer from insufficient annotation and a lack of standardization, which reduces the effectiveness of AI-driven assessments in forecasting drug-like characteristics.[62]

Computational versus Experimental Validation.

Although artificial intelligence has significantly sped up the identification of bioactive compounds, the shift from computational discovery to experimental validation presents a considerable obstacle. Drug candidates produced through AI must be subjected to chemical synthesis, biological assessments, and pharmacokinetic analysis, all of which necessitate thorough confirmation in a laboratory setting.[63] Additionally, AI models might misunderstand intricate biological interactions, highlighting the need for human supervision and experimental validation through cross-checking.[45]

Future Research Directions

Integrating AI with Synthetic Biology for Improved Drug Production

Integrating artificial intelligence with synthetic biology has the potential to transform the production of microbial drugs by facilitating precise modifications to biosynthetic pathways. Utilizing AI-based predictive modeling can assist in activating gene clusters, leading to enhanced optimization of microbial strains for increased yields and better bioavailability.[64,65] For example, genetic alterations utilizing CRISPR technology in *Streptomyces* species have improved the yield of doxorubicin analogs while minimizing toxicity.[66]

Investigating Soil Microbiomes in Extreme Habitats for Unique Compounds

Soil microbiomes found in harsh environments, including deserts, deep-sea sediments, and Arctic permafrost, present a valuable yet underutilized source of unique bioactive compounds.[64,65] Microorganisms inhabiting these environments have developed distinct metabolic adaptations, which may result in the identification of novel categories of anticancer agents.[66,67] Advancements in next-generation sequencing and metagenomics can enhance the detection of rare and uncultivable microorganisms, thereby broadening the pipeline for discovering natural product drugs.[45,63,65]

Clinical Translation of AI-Discovered Microbial Drugs

To connect AI-based discovery with clinical use, upcoming research must prioritize the speed of preclinical validation and the execution of clinical trials for compounds derived from microbes. Establishing standardized AI frameworks for predicting drug-likeness, evaluating toxicity, and profiling pharmacokinetics could improve the success rates of candidates identified through AI methods.[68] Collaborations among AI researchers, microbiologists, and the pharmaceutical sector will be crucial for accelerating the transition of promising compounds into clinical applications.[66-68]

CONCLUSION

Soil microorganisms constitute a significant but largely untapped source for the identification of new anticancer pharmaceuticals. Historically, compounds derived from microbes, including doxorubicin, mitomycin C, and bleomycin, have transformed chemotherapy by providing highly effective therapies for various types of cancers.[12,69] The complete capabilities of soil microbes are still largely unexploited, primarily because of the intricate

biosynthetic processes, limited production yields, and difficulties associated with large-scale manufacturing.[70] Advancements in metagenomics, synthetic biology, and bioinformatics are revealing microbial secondary metabolites that were once difficult to access, thus creating new possibilities for the development of cancer medications.[71] The incorporation of Artificial Intelligence (AI) into the process of drug discovery has significantly improved the capacity to discover, refine, and repurpose compounds derived from microbes for cancer treatment. Techniques such as AI-driven genome mining, virtual screening, and predictive modeling have expedited the identification of new bioactive substances, thereby minimizing both the time and expenses linked to conventional drug development methods.[70-72] Additionally, tools that utilize artificial intelligence have greatly enhanced the accuracy of predicting drug-target interactions and toxicity, thereby raising the success rate of candidates derived from microbes in both preclinical and clinical trials.[72,73] One of the most encouraging features of drugs derived from microbes is their ability to address chemotherapy resistance. The rise of Multi-Drug Resistance (MDR) in cancer cells, caused by factors such as efflux pumps, improved DNA repair mechanisms, and the evasion of apoptosis, continues to pose a significant obstacle in cancer treatment.[12,70] Numerous secondary metabolites produced by microbes have shown the capacity to circumvent or suppress these resistance mechanisms, positioning them as promising options for combination therapies or as independent treatments for resistant cancers.[71]

Implications for Oncology and Drug Development

The combination of anticancer agents derived from soil, AI-enhanced drug discovery, and precision oncology necessitates a collaborative approach involving oncologists, microbiologists, bioinformaticians, and synthetic biologists. Strategies for future drug development should prioritize:

- The enhancement of metagenomic and AI-supported screening methods to discover new microbial-derived compounds with anticancer effects.

- The refinement of microbial biosynthetic pathways via genetic engineering and synthetic biology to increase the yield and stability of drugs.[70,72]

- Enhancing clinical translation through the incorporation of AI-driven toxicity evaluations, pharmacokinetic simulations, and focused drug delivery methods.

- Creating combination therapies that leverage microbial-derived substances to improve the effectiveness of current chemotherapeutic drugs and address resistance strategies.

- By promoting interdisciplinary collaboration, researchers can fully harness the therapeutic capabilities of microbial-derived anticancer compounds, paving the way for more efficient, targeted, and individualized cancer treatment options.[12,70,73]

Final Thoughts

The future of cancer treatment may be found at the convergence of nature and technology. Soil microorganisms present a biologically rich source of anticancer substances, while advancements in artificial intelligence have opened up new avenues for efficient drug development and refinement. By merging research on natural products with state-of-the-art computational techniques, scientists have the potential to transform oncology, delivering innovative and more effective therapies for patients globally. As progress continues to connect microbiology, AI, and cancer treatment modalities, the forthcoming generation of anticancer drugs derived from microbes could be instrumental in addressing existing treatment challenges, heralding a new phase in precision medicine.[45,62,64,66,71-73]

ACKNOWLEDGEMENT

The author expresses gratitude to the Faculty of Medicine at King Abdulaziz University, Rabigh, Saudi Arabia, for academic support and guidance during the research process.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AI: Artificial Intelligence; **MDR:** Multidrug Resistance; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **DNA:** Deoxyribonucleic Acid; **RNA:** Ribonucleic Acid; **VEGF:** Vascular Endothelial Growth Factor; **EAS:** External Anal Sphincter; **IAS:** Internal Anal Sphincter; **CSCs:** Cancer Stem Cells; **DDR:** DNA Damage Response; **EPIs:** Efflux Pump Inhibitors; **MRSA:** Methicillin-Resistant *Staphylococcus aureus*; **mVOCs:** Microbial Volatile Organic Compounds; **ML:** Machine Learning; **DL:** Deep Learning; **RND:** Resistance Nodulation Division; **MFS:** Major Facilitator Superfamily.

REFERENCES

1. Catalani E, Proietti Serafini F, Zecchini S, Picchietti S, Fausto AM, Marcantoni E, *et al.* Natural products from aquatic eukaryotic microorganisms for cancer therapy: perspectives on anti-tumour properties of ciliate bioactive molecules. Pharmacol Res. 2016; 113(A):409-20. doi: 10.1016/j.phrs.2016.09.018, PMID 27650755.
2. Yuan R, Hou Y, Sun W, Yu J, Liu X, Niu Y, *et al.* Natural products to prevent drug resistance in cancer chemotherapy: a review. Ann N Y Acad Sci. 2017; 1401(1): 19-27. doi: 10.1111/nyas.13387, PMID 28891091.
3. Talib WH, Alsayed AR, Barakat M, Abu-Taha MI, Mahmod AI. Targeting drug chemo-resistance in cancer using natural products. Biomedicines. 2021; 9(10): 1353. doi: 10.3390/biomedicines9101353, PMID 34680470.
4. Demain AL, Vaishnav P. Natural products for cancer chemotherapy. Microb Biotechnol. 2011; 4(6): 687-99. doi: 10.1111/j.1751-7915.2010.00221.x, PMID 21375717.
5. Efferth T, Saeed ME, Kadioglu O, Seo EJ, Shirooie S, Mbaveng AT, *et al.* Collateral sensitivity of natural products in drug-resistant cancer cells. Biotechnol Adv. 2020; 38: 107342. doi: 10.1016/j.biotechadv.2019.01.009, PMID 30708024.
6. Zou JY, Chen QL, Luo XC, Damdinjav D, Abdelmohsen UR, Li HY, *et al.* Natural products reverse cancer multidrug resistance. Front Pharmacol. 2024; 15: 1348076. doi: 10.3389/fphar.2024.1348076, PMID 38572428.
7. Lu S, Wang C, Ma J, Wang Y. Metabolic mediators: microbial-derived metabolites as key regulators of anti-tumor immunity, immunotherapy, and chemotherapy. Front Immunol. 2024; 15: 1456030. doi: 10.3389/fimmu.2024.1456030, PMID 39351241.

8. Wu J, Li Y, He Q, Yang X. Exploration of the use of natural compounds in combination with chemotherapy drugs for tumor treatment. Molecules. 2023; 28(3): 1022. doi: 10.3390/molecules28031022, PMID 36770689.
9. Chen T, Xiao Z, Liu X, Wang T, Wang Y, Ye F *et al.* Natural products for combating multidrug resistance in cancer. Pharmacol Res. 2024; 202: 107099. doi: 10.1016/j.phrs.2024.107099, PMID 38342327.
10. Deb D, Danino T. Abstract 2186: Bacterial lung cancer therapeutics from soil bacteria in New York City. Cancer Res. 2024; 84(6_Supplement):Abstract 2186:. doi: 10.1158/1538-7445.AM2024-2186.
11. Li G, Lin P, Wang K, Gu CC, Kusari S. Artificial intelligence-guided discovery of anticancer lead compounds from plants and associated microorganisms. Trends Cancer. 2022; 8(1): 65-80. doi: 10.1016/j.trecan.2021.10.002, PMID 34750090.
12. Al-Tuwaijri M. Phylogenetic analysis and bioactivity of soil-derived Nocardiopsis species: antibacterial and anticancer potentials against MCF7 and HCT16 cell. J Biosci Appl Res. 2023: 102-14. doi: 10.21608/jbaar.2023.314704.
13. De Castilhos J, Tillmanns K, Blessing J, Laraño A, Borisov V, Stein-Thoeringer CK. Microbiome and pancreatic cancer: time to think about chemotherapy. Gut Microbes. 2024; 16(1): 2374596. doi: 10.1080/19490976.2024.2374596, PMID 39024520.
14. Zhang T, Deng Y, Liu YS, Chua SL, Tang BZ, Khoo BL. Bacterial targeted AIE photosensitizers synergistically promote chemotherapy for the treatment of inflammatory cancer. Chem Eng J. 2022; 447. doi: 10.1016/j.cej.2022.137579.
15. Chow R, Midroni J, Kaur J, Boldt G, Liu G, Eng L, *et al.* Use of artificial intelligence for cancer clinical trial enrolment: A systematic review and meta-analysis. J Natl Cancer Inst. 2023; 115(4): 365-74. doi: 10.1093/jnci/djad013, PMID 36688707.
16. Kanan M, Alharbi H, Alotaibi N, Almasuood L, Aljoaid S, Alharbi T, *et al.* AI-driven models for diagnosing and predicting outcomes in lung cancer: A systematic review and meta-analysis. Cancers. 2024; 16(3): 674. doi: 10.3390/cancers16030674, PMID 38339425.
17. Kang HS, Brady SF. Arimetamycin A: improving clinically relevant families of natural products through sequence-guided screening of soil metagenomes. Angew Chem Int Ed Engl. 2013; 52(42): 11063-7. doi: 10.1002/anie.201305109, PMID 24038656.
18. Sharrar AM, Crits-Christoph A, Méheust R, Diamond S, Starr EP, Banfield JF. Bacterial secondary metabolite biosynthetic potential in soil varies with phylum, depth, and vegetation type. mBio. 2020; 11(3): e00416-20. doi: 10.1128/mBio.00416-20, PMID 32546614.
19. Mirzaee H, Ariens E, Blaskovich MA, Clark RJ, Schenk PM. Biostimulation of bacteria in liquid culture for identification of new antimicrobial compounds. Pharmaceuticals (Basel). 2021; 14(12): 1232. doi: 10.3390/ph14121232, PMID 34959632.
20. Qadir M, Hussain A, Iqbal A, Shah F, Wu W, Cai H. Microbial utilization to nurture robust agroecosystems for food security. Agronomy. 2024; 14(9).doi: 10.3390/agronomy14091891.
21. Al-Amoudi S, Essack M, Simões MF, Bougouffa S, Soloviev I, Archer JA, *et al.* Bioprospecting Red Sea Coastal Ecosystems for culturable microorganisms and Their antimicrobial Potential. Mar Drugs. 2016; 14(9): 165. doi: 10.3390/md14090165, PMID 27626430.
22. Yahya G, Ebada A, Khalaf EM, Mansour B, Nouh NA, Mosbah RA, *et al.* Soil-associated Bacillus species: A reservoir of bioactive compounds with potential therapeutic activity against human pathogens. Microorganisms. 2021; 9(6): 1131. doi: 10.3390/microorganisms9061131, PMID 34073963.
23. Dharavath R, A, S. Employing soil isolated fungi for production of bioactive phenolic compounds: a fermentative approach. Prep Biochem Biotechnol. 2024: 1-11. doi: 10.1080/10826068.2024.2326882.
24. Pan I, Nanjundan K, Achuthan A, Issac PK, Rajagopal R, Chang SW, *et al.* Exploration of compost soil for the production of thermo-stable Bacillus protease to synthesize bioactive compounds through soy protein hydrolysis. Agronomy. 2023; 13(4). doi: 10.3390/agronomy13041019.
25. De Boer W, Li X, Meisner A, Garbeva P. Pathogen suppression by microbial volatile organic compounds in soils. FEMS Microbiol Ecol. 2019; 95(8): fiz105. doi: 10.1093/femsec/fiz105, PMID 31265069.
26. Chabner BA, Roberts TG. Timeline: Chemotherapy and the war on cancer. Nat Rev Cancer. 2005; 5(1): 65-72. doi: 10.1038/nrc1529, PMID 15630416.
27. Tomasz M. Mitomycin C: small, fast and deadly (but very selective). Chem Biol. 1995; 2(9): 575-9. doi: 10.1016/1074-5521(95)90120-5, PMID 9383461.
28. Hecht SM. Bleomycin: new perspectives on the mechanism of action. J Nat Prod. 2000; 63(1): 158-68. doi: 10.1021/np990549f, PMID 10650103.
29. Colis LC, Woo CM, Hegan DC, Li Z, Glazer PM, Herzon SB. The cytotoxicity of (-)-lomaiviticin A arises from induction of double-strand breaks in DNA. Nat Chem. 2014; 6(6): 504-10. doi: 10.1038/nchem.1944, PMID 24848236.
30. Gupta PB, Onder TT, Jiang G, Tao K, Kuperwasser C, Weinberg RA, *et al.* Identification of selective inhibitors of cancer stem cells by high-throughput screening. Cell. 2009; 138(4): 645-59. doi: 10.1016/j.cell.2009.06.034, PMID 19682730.
31. Azad AK, Campbell KR, Zhabyeyev P, Oudit GY, Moore RB, Murray AG. Loss of apelin blocks the emergence of sprouting angiogenesis in experimental tumors. FASEB J. 2022; 36(10): e22560. doi: 10.1096/fj.202200616RR, PMID 36165236.
32. Wijesekara I, Zhang C, Van Ta Q, Vo TS, Li YX, Kim SK. Physcion from marine-derived fungus Microsporum sp. induces apoptosis in human cervical carcinoma HeLa cells. Microbiol Res. 2014; 169(4): 255-61. doi: 10.1016/j.micres.2013.09.001, PMID 24071573.
33. Herzon SB. The mechanism of action of (-)-lomaiviticin A. Acc Chem Res. 2017; 50(10): 2577-88. doi: 10.1021/acs.accounts.7b00347, PMID 28956437.
34. Chen HY, Chiang YF, Huang CY, Shieh TM, Kao C, Chang FK, *et al.* Spirulina phycocyanin extract and its active components suppress epithelial-mesenchymal transition process in endometrial cancer via targeting TGF-beta1/SMAD4 signaling pathway. Biomed Pharmacother. 2022; 152: 113219. doi: 10.1016/j.biopha.2022.113219, PMID 35691155.
35. Zhao Y, Adjei AA. Targeting angiogenesis in cancer therapy: moving beyond vascular endothelial growth factor. Oncologist. 2015; 20(6): 660-73. doi: 10.1634/theoncologist.2014-0465, PMID 26001391.
36. Qureshi R, Irfan M, Gondal TM, Khan S, Wu J, Hadi MU, *et al.* AI in drug discovery and its clinical relevance. Heliyon. 2023; 9(7): e17575. doi: 10.1016/j.heliyon.2023.e17575, PMID 37396052.
37. Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, *et al.* Applications of machine learning in drug discovery and development. Nat Rev Drug Discov. 2019; 18(6): 463-77. doi: 10.1038/s41573-019-0024-5, PMID 30976107.
38. Patel L, Shukla T, Huang X, Ussery DW, Wang S. Machine learning methods in drug discovery. Molecules. 2020; 25(22): 5277. doi: 10.3390/molecules25225277, PMID 33198233.
39. Ekins S, Puhl AC, Zorn KM, Lane TR, Russo DP, Klein JJ, *et al.* Exploiting machine learning for end-to-end drug discovery and development. Nat Mater. 2019; 18(5): 435-41. doi: 10.1038/s41563-019-0338-z, PMID 31000803.
40. Jiménez-Luna J, Grisoni F, Weskamp N, Schneider G. Artificial intelligence in drug discovery: recent advances and future perspectives. Expert Opin Drug Discov. 2021; 16(9): 949-59. doi: 10.1080/17460441.2021.1909567, PMID 33779453.
41. Brizuela CA, Liu G, Stokes JM, De La Fuente-Nunez C. AI methods for antimicrobial peptides: progress and challenges. Microb Biotechnol. 2025; 18(1): e70072. doi: 10.1111/1751-7915.70072, PMID 39754551.
42. Deng J, Yang Z, Samaras D, Wang F. Artificial intelligence in drug discovery: applications and techniques. Brief Bioinform. 2021. doi: 10.1093/bib/bbab430.
43. David L, Thakkar A, Mercado R, Engkvist O. Molecular representations in AI-driven drug discovery: a review and practical guide. J Cheminform. 2020; 12(1): 56. doi: 10.1186/s13321-020-00460-5, PMID 33431035.
44. Lin Y, Zhang Y, Wang D, Yang B, Shen YQ. Computer especially AI-assisted drug virtual screening and design in traditional Chinese medicine. Phytomedicine. 2022; 107: 154481. doi: 10.1016/j.phymed.2022.154481, PMID 36215788.
45. Han R, Yoon H, Kim G, Lee H, Lee Y. Revolutionizing medicinal chemistry: the application of artificial intelligence (AI) in early drug discovery. Pharmaceuticals (Basel). 2023; 16(9): 1259. doi: 10.3390/ph16091259, PMID 37765069.
46. Chen W, Liu X, Zhang S, Chen S. Artificial intelligence for drug discovery: resources, methods, and applications. Mol Ther Nucleic Acids. 2023; 31: 691-702. doi: 10.1016/j.omtn.2023.02.019, PMID 36923950.
47. Liu J, Du H, Huang L, Xie W, Liu K, Zhang X, *et al.* AI-powered microfluidics: shaping the future of phenotypic drug discovery. ACS Appl Mater Interfaces. 2024; 16(30): 38832-51. doi: 10.1021/acsami.4c07665, PMID 39016521.
48. 48. 48. Garcia-Mayea Y, Mir C, Masson F, Paciucci R, Lleonart ME. Insights into new mechanisms and models of cancer stem cell multidrug resistance. Semin Cancer Biol. 2020; 60: 166-80. doi: 10.1016/j.semcancer.2019.07.022, PMID 31369817.
49. Stefanko E, Wróbel T. Mechanisms of resistance to cancer chemotherapy. Adv Clin Exp Med. 2010; 19: 5-12.
50. Li Y, Wang Z, Ajani JA, Song S. Drug resistance and Cancer stem cells. Cell Commun Signal. 2021; 19(1): 19. doi: 10.1186/s12964-020-00627-5, PMID 33588867.
51. Cojoc M, Mäbert K, Muders MH, Dubrovska A. A role for cancer stem cells in therapy resistance: cellular and molecular mechanisms. Semin Cancer Biol. 2015; 31: 16-27. doi: 10.1016/j.semcancer.2014.06.004, PMID 24956577.
52. Halder K. Chemotherapy resistance in cancer: mechanism and roadmap to evade exploring apoptosis. IJALSR. 2024; 7(2): 17-40. doi: 10.31632/ijalsr.2024.v07i02.003.
53. Safa AR. Drug and apoptosis resistance in cancer stem cells: a puzzle with many pieces. Cancer Drug Resist. 2022; 5(4): 850-72. doi: 10.20517/cdr.2022.20, PMID 36627897.
54. Lowrence RC, Subramaniapillai SG, Ulaganathan V, Nagarajan S. Tackling drug resistance with efflux pump inhibitors: from bacteria to cancerous cells. Crit Rev Microbiol. 2019; 45(3): 334-53. doi: 10.1080/1040841X.2019.1607248, PMID 31248314.
55. Holmes AR, Cardno TS, Strouse JJ, Ivnitski-Steele I, Keniya MV, Lackovic K, *et al.* Targeting efflux pumps to overcome antifungal drug resistance. Future Med Chem. 2016; 8(12): 1485-501. doi: 10.4155/fmc-2016-0050, PMID 27463566.
56. Garcia ÍR, De Oliveira Garcia FA, Pereira PS, Coutinho HD, Siyadatpanah A, Norouzi R, *et al.* Microbial resistance: the role of efflux pump superfamilies and their respective substrates. Life Sci. 2022; 295: 120391. doi: 10.1016/j.lfs.2022.120391, PMID 35149116.
57. Kaur B, Gupta J, Sharma S, Sharma D, Sharma S. Focused review on dual inhibition of quorum sensing and efflux pumps: A potential way to combat multi drug resistant *Staphylococcus aureus* infections. Int J Biol Macromol. 2021; 190: 33-43. doi: 10.1016/j.ijbiomac.2021.08.199, PMID 34480904.
58. Zhang Z, Zhang L, Zhang L, Chu H, Zhou J, Ju F. Diversity and distribution of biosynthetic gene clusters in agricultural soil microbiomes. mSystems. 2024; 9(4): e0126323. doi: 10.1128/msystems.01263-23, PMID 38470142.

59. Baral B, Akhgari A, Metsä-Ketelä M. Activation of microbial secondary metabolic pathways: avenues and challenges. Synth Syst Biotechnol. 2018; 3(3): 163-78. doi: 10 .1016/j.synbio.2018.09.001, PMID 30345402.
60. Duan FL, Duan CB, Xu HL, Zhao XY, Sukhbaatar O, Gao J, *et al.* AI-driven drug discovery from natural products. Adv Agrochem. 2024; 3(3): 185-7. doi: 10.1016/j.a ac.2024.06.003.
61. Xue HT, Stanley-Baker M, Kong AW, Li HL, Goh WW. Data considerations for predictive modeling applied to the discovery of bioactive natural products. Drug Discov Today. 2022; 27(8): 2235-43. doi: 10.1016/j.drudis.2022.05.009, PMID 35577232.
62. Gangwal A, Lavecchia A. Artificial intelligence in natural product drug discovery: current applications and future perspectives. J Med Chem. 2025; 68(4): 3948-69. doi: 10.1021/acs.jmedchem.4c01257, PMID 39916476.
63. Walters WP, Barzilay R. Critical assessment of AI in drug discovery. Expert Opin Drug Discov. 2021; 16(9): 937-47. doi: 10.1080/17460441.2021.1915982, PMID 33870801.
64. Hill A, True JM, Jones CH. Transforming drug development with synthetic biology and AI. Trends Biotechnol. 2024; 42(9): 1072-5. doi: 10.1016/j.tibtech.2024.01.008, PMID 38383215.
65. Bülbül EF, Bode HB, Schmitt S, Bozhüyük KA. Engineering the future of medicine: natural products, synthetic biology and artificial intelligence for next-generation therapeutics for next41.2021.1915982..org/10.1016/j.aac.2024.06.003.003.ions. Internationtps. 2025; 15(2): e70146. doi: 10.1002/ctm2.70146, PMID 39856487.
66. Vora LK, Gholap AD, Jetha K, Thakur RR, Solanki HK, Chavda VP. Artificial intelligence in pharmaceutical technology and drug delivery design. Pharmaceutics. 2023; 15(7): 1916. doi: 10.3390/pharmaceutics15071916, PMID 37514102.
67. De Almeida AF, Moreira R, Rodrigues T. Synthetic organic chemistry driven by artificial intelligence. Nat Rev Chem. 2019; 3(10): 589-604. doi: 10.1038/s41570-019-0124-0.
68. D, Artificial intelligence in biology. Int J Multidiscip Res. 2024; 6(2). doi: 10.36948/ijf mr.2024.v06i02.15067.
69. Pettit RK. Soil DNA libraries for anticancer drug discovery. Cancer Chemother Pharmacol. 2004; 54(1): 1-6. doi: 10.1007/s00280-004-0771-8, PMID 15071757.
70. Yadav RP, Bhattarai BR, Budhathoki R, Budthapa P, Rana M, Magar RT, *et al.* Metabolites profiling of soil Actinomycetes with antimicrobial and anticancer activities. Nepal J Biotechnol. 2024; 12(2): 151-68. doi: 10.54796/njb.v12i2.329.
71. Borsetto C, Amos GC, Da Rocha UN, Mitchell AL, Finn RD, Laidi RF, *et al.* Microbial community drivers of PK/NRP gene diversity in selected global soils. Microbiome. 2019; 7(1): 78. doi: 10.1186/s40168-019-0692-8, PMID 31118083.
72. Niazi SK, Basavarajappa DS, Kumaraswamy SH, Bepari A, Hiremath H, Nagaraja SK, *et al.* GC-MS based characterization, antibacterial, antifungal and anti-oncogenic activity of ethyl acetate extract of Aspergillus niger Strain AK-6 isolated from rhizospheric soil. Curr Issues Mol Biol. 2023; 45(5): 3733-56. doi: 10.3390/cimb4505 0241, PMID 37232710.
73. Diao Z, Jing X, Hou X, Meng Y, Zhang J, Wang Y, *et al.* Artificial intelligence-assisted automatic Raman-activated cell sorting (AI-RACS) system for mining specific functional microorganisms in the microbiome. Anal Chem. 2024; 96(46): 18416-26. doi: 10.1021/acs.analchem.4c03213, PMID 39526454.

Cite this article: Albukhari AF. Soil Microorganisms in Cancer Therapy: AI-Driven Drug Discovery, Natural Compounds, and Strategies to Overcome Chemotherapy Resistance-Oil Microorganisms. Pharmacog Rev. 2025;19(38):234-46.