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Advancements in Computational Drug Design and Natural Therapeutics: A Systematic Review of Emerging Strategies

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ABSTRACT

Objective: *The growing prevalence of chronic diseases, including cancer, and the rise of drug resistance highlight the urgent need for novel, effective, and safer therapeutic strategies. There is an abounding history of the use of natural products, which are derived from plants, fungi, and microorganisms. Modern tools, such as computational drug design, in silicon modeling and high-throughput screening have been integrated with natural products for drug discovery in recent years.* ***Methods:*** *This review discusses the juxtaposition of natural products towards modern drug discovery with specific interest to cancer and other diseases. An overview of computational drug design strategies, such as molecular docking, time-domain simulations, and quantitative structure-activity relationship (QSAR) applied to natural compounds is revived. Additionally, it discusses high-throughput screening and bioinformatics methods that can aid in the identification and optimization of natural drug candidates.* ***Results:*** *The combined implementation with computational methods and natural products is speeding up the identification of potential drug candidates, with increased bioavailability and less toxicity. Moreover, the integration of personalized medicine and nanotechnology in this domain has been shown to improve their therapeutic potential and biodistribution, providing more effective and tailored treatment options for diseases such as cancer and cardiovascular disorders also.* ***Novelty:*** *The plant origin of the compound and its traditional therapeutic use make it an interesting alternative coupled to modern technologies of drug discovery. Through overcoming challenges related to bioavailability and toxicity; while integrating advanced techniques such as nanotechnology and personalized medicine.*

INTRODUCTION

The current health challenges, such as the epidemic of chronic diseases; antibiotic resistance; and growing cancer rates in humans necessitate searching for new methods of treatment that are effective yet safer. Natural products have been established as one of the main sources of drug candidates among all potential therapeutic options. Even today, traditional medicine uses natural compounds. As recognized, particularly phytochemicals from these natural products (i.e., curcumin, resveratrol, EGCG and genistein) exhibit promising biological effects related to anticancer, anti-inflammation, antioxidant and antimicrobial responsibilities [1], [2].

Natural products have potential beyond oncological diseases. They have shown therapeutic potentials for a broad spectrum of diseases including cardiovascular diseases, diabetes, neurological disorders and infections. There is an increasing interest in natural products; however, only little focus on modern scientific techniques directed to understand their molecular mechanisms of action and therapeutic potentials. In this regard, the computational drug design (modeling of bioactive compounds using in silico

modeling) as well as high-throughput screening (HTS) have become key players with respect to speeding up drug discovery and optimizing natural compound use [3], [4].

Computational drug design is the process by which the natural activity of compounds in biological systems can be predicted using computer-based methods. It entails using tools such as molecular docking, molecular dynamics simulations and quantitative structure-activity relationship (QSAR) modeling to simulate a natural compound in the context of its target proteins and cellular pathways. These computational methods enable a more rapid and refined screening of drug candidates, as well as greater insights into their mechanisms of action [5], [6].

Besides computational approaches, the combination of bioinformatics and pharmacogenomics has also created various possibilities for personalized medicine. The field of personalized medicine aims to customize medical treatment for each individual based on their genetic background so that patients receive the most appropriate and effective therapies [7]. The potential of natural products in personalized medicine is particularly exciting, because these compounds can be chosen and tailored to hit much of the specific genetic variation responsible for diseases such as cancer, diabetes and cardiovascular diseases. This approach helps to identify the best possible treatment for an individual patient, thereby optimizing clinical outcomes and minimizing side effects based on genomic data and bioinformatics [8].

In particular natural product drug discovery has witnessed significant progress, driven by advances in structural biology and high-throughput screening (HTS). Techniques from structural biology (like X-ray crystallography and cryogenic electron microscopy, or Cryo-EM) produced detailed three-dimensional views of proteins that have enabled scientists to design drugs capable of binding to precise targets [9]. High-throughput screening enables the testing of massive compound collections, even natural products, for molecules with strong biological activity. Using HTS in conjunction with structural biology has enabled rapid exploration of drug candidates from botanicals [10].

Bioavailability and toxicity profile optimization are among the major obstacles in drug discovery of natural products. Despite the potent biological activities, clinical application of many natural compounds was limited due to their poor bioavailability or potential toxicity [11]. An innovative approach to overcome these obstacles relies on nanotechnology and drug delivery systems for enhancing the pharmacokinetics of natural products. Moreover, nanoparticles and nanocarriers can thereby facilitate the absorption of natural compounds in vivo and transport them to target sites specifically, e.g., cancer cells without affecting normal tissues. Such an approach is expected to greatly enhance the therapeutic efficacy of natural products and reduce side effects [3].

This Review discusses the importance of natural products in drug discovery, with a focus on cancer and disease applications. Natural compounds have not only been researched and developed in laboratories but computational drug design, in silico modeling, and recent technologies such as high-throughput screening and bioinformatics are perfect biological tools to discover new leads [11]. We will also discuss the state-of-

art in personalized medicine and nanotechnology that are overcoming the limitations of natural products, making them useful for targeted and effective therapies.

This article tries to characterize the potential for new therapeutic strategies that natural products can provide for drug development by collating some leading work combining modern drug discovery approaches with those based upon the continued renaissance of knowledge gained from natural product drug discovery efforts.

RESEARCH METHOD

Data Collection Process

Data collection was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Data were collected through a comprehensive search strategy from after the peer-review journals and significant academic databases such as PubMed, Scopus, Google scholar. Keywords and inclusion criteria based on the research questions were developed. Following the construction of the search strategy, studies were screened for title and abstract. Studies that passed the first round of screening based on title and abstract review were included for full-text review.

The inclusion criteria were well pacified, comprising studies published within the previous ten years, written in English language, and related to therapeutic effect of natural compounds. Key information, including details of sample size, research methodology, outcomes and summary/conclusions were extracted from the included studies. Moreover, a quality assessment was conducted to assess the validity and reliability of the studies included. Main idea: The PRISMA flow diagram represents the collected data synthesis and analysis process. Adhering to the PRISMA guidelines also guaranteed that the data was collected in a comprehensive, objective, and replicable manner, establishing a structured framework for further analysis.

Selection Criteria

Research selection workflow was in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) instructions. Relevant studies were collected through specific keywords in PubMed, Scopus and Google Scholar databases, a total of 500 articles were advanced. After that, 150 studies were chosen for complete text review through the screening among titles and abstracts (Figure 1).

Based on inclusion and exclusion criteria, 50 studies were included after each of the full-text review. 100 studies not related to natural products, specific research questions or with inadequate general quality were excluded. In the end, 50 studies were identified that met inclusion criteria and were of adequate quality for further analysis and data extraction. This approach provided a selection of studies for this analysis that were appropriate and of good quality.

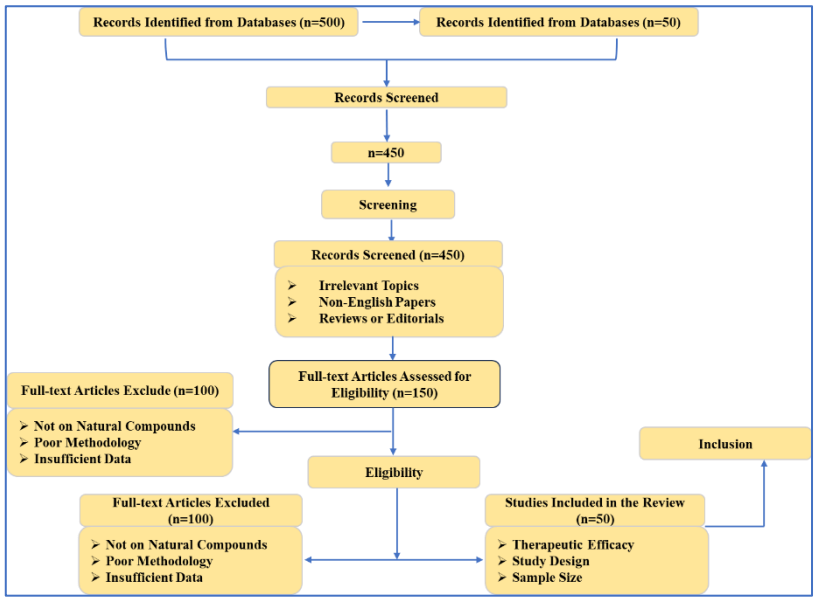


Figure 1. PRISMA flow diagram illustrating the study selection process. The diagram shows the number of records identified, screened, assessed for eligibility, and ultimately included in the final analysis based on predefined inclusion and exclusion criteria.

Computational Drug Design: Core Methodologies and Technological Innovations

A. Overview of Computational Approaches

Computational drug design (or in silico drug design) is a science-based approach to using computational models and algorithms to predict the behavior and effectiveness of drug molecules. This is mainly based on structure and ligand-based methods. In structure-based approaches, the researchers investigate the three-dimensional structure of potential target proteins and use this information to design molecules that can interact effectively with the protein [12], [13]. In ligand-based methodologies, the interaction of drug molecules with their respective target proteins is identified through previously established interactions between ligands and receptors. These computational methods allow scientists to discover formal medication candidates in a dramatically quicker timeframe while assessing their usefulness at the moment they undergo clinical trials [14].

Currently, computational techniques are empowered by cutting-edge methods for molecular docking, molecular dynamics simulations, and quantitative structure-activity relationship (QSAR) modeling. The best binding interactions are predicted by molecular docking, i.e., the prediction of the notion of whether a drug molecule will bind to a target protein [15]. Molecular dynamics simulations are utilized to study the dynamic properties of drug molecules and their target proteins, enabling better understanding of their binding affinities, structural conformations, stability, and interaction patterns. A queer structure–activity relationship (QSAR) model predicting biological activity from a compound's chemical structure. The use of these methods has significantly increased the efficiency, accuracy, and rapidity of drug design, leading to more precise and effective approaches to pharmaceutics [16].

B. Recent Technological Breakthroughs

Over the past few years, there have been tremendous advancements in computational drug design technologies that reshaped the entire process (Figure 2). While the use of Artificial Intelligence (AI) and Machine Learning (ML) has revolutionized drug design techniques. This led to the development of AI and ML algorithms, which can accurately predict the potential efficacy and effects of molecules much faster than before [17]. More precisely, deep learning and neural networks, which extract conclusions from extensive sets of data, have brought revolutionary change in identifying novel drug candidates. These technologies provide researchers with faster and more efficient ways to evaluate new compounds, structures, and targets.

Furthermore, Cryo-Electron Microscopy (Cryo-EM) and Structural Bioinformatics have unprecedented impact on drug discovery. Cryo-EM allows researchers to obtain the most detailed and accurate three-dimensional structures of proteins, helping understand protein-ligand interactions [18]. These advanced technologies contribute to high-quality structural models for drug design, predicting the dynamics, stability, and functionality of drug-ROMP compounds. With the application of these technologies, computational drug design has been achieved to a more sophisticated level, higher in pace and productivity, that will be imperative for future advancements in drug development [8].

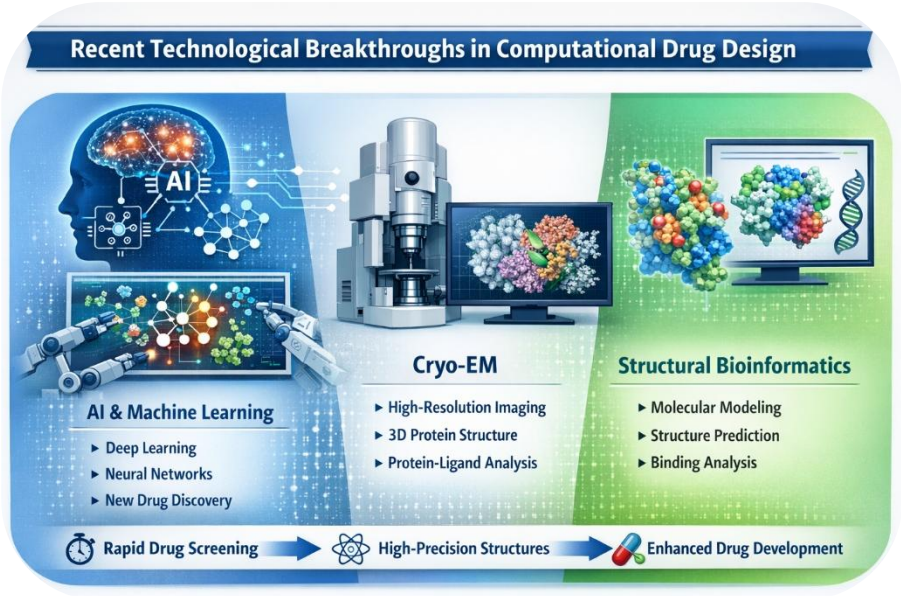


Figure 2. Technological advancements in computational drug design, showcasing AI & Machine Learning, Cryo-EM, and Structural Bioinformatics in accelerating drug discovery and development.

C. Applications in Drug Discovery

Computational methodologies are of paramount importance from multiple aspects of drug discovery, with a particular focus on novel drug candidate identification, target validation, and performance assessment (Table 1). Molecular docking is extensively used in the initial steps of drug design, as it predicts very reliable interactions and binding site conformations for the ligands on the target proteins [19]. Using molecular dynamics, one

can also study the dynamic interaction of drugs and proteins, which plays a crucial role in the prediction of drug stability and potential side effects.

In addition, use of Quantitative Structure-Activity Relationship (QSAR) models to assess the relationship between chemical structure and biological activity of a drug has made the design and development of new, fit-for-purpose compounds faster [15], [18]. All these computational methods work together to accelerate the process of discovering new drugs, making it not only faster and more efficient but also cheaper, which contributes towards better-targeting medicines for respective ailments.

Table 1. Applications of Computational Methods in Drug Discovery.

Computational Method	Application	Benefits	Specific Features	Additional Aspects	References
Molecular Docking	Predicting interactions between drug molecules and target proteins	Rapid molecular screening, target identification	Accurate binding positions and interactions	Quick identification of potential drug efficacy	[20]
Molecular Dynamics	Analyzing the dynamic behavior of drugs and proteins	Predicts stability and potential side effects	Study of protein conformation and drug behavior	Helps assess toxicity and side effects	[21]
QSAR (Quantitative Structure-Activity Relationship)	Determining the relationship between chemical structure and biological activity	Accelerates drug design and identification of new compounds	Provides predictions on drug efficacy and structure	Helps design and develop new drug candidates	[15]
ADME & PK/PD Modeling	Analyzing drug absorption, metabolism, distribution, and excretion (ADME)	Improves drug efficacy and safety	Determines pharmacokinetic (ADME) and pharmacodynamic (PK/PD) data	Measures drug safety and effectiveness	[16]
De Novo Drug Design	Designing new drug candidates from scratch	Creates new drug candidates for	Uses algorithms to design new drug molecules from scratch	Useful for designing drugs for new and	[22]

	unexplored targets	unknown targets

RESULTS AND DISCUSSION

Natural Therapeutics in Modern Drug Design

A. Role of Natural Products

Phytochemicals—or natural compounds found inside of plants that provide a variety of health benefits. Phytochemicals have various properties, among which anticancer is considered an important one (Figure 3). Several different phytochemicals, such as curcumin, resveratrol, genistein, EGCG, and I3C, have antioxidant properties that may help prevent cancer from forming [23], [24]. These naturally occurring compounds inhibit the number of cancer cells and restrict their dissemination, or metastasizing, to other sites in the body.

The potential health benefits of phytochemicals are primarily attributed to their antioxidant, anti-inflammatory, and anticancer effects. As an example, curcumin, one of the natural anti-inflammatories, is known to be able to inhibit cancer cell processes [6], [25]. By the same token, resveratrol and EGCG act by diminishing free radical damage as well as adsorbing cancer cell proliferation. There is copious evidence that these phytochemicals are not only involved in cell division and tumor promotion but also strengthen the immune system of the body, rendering them promising drug candidates against cancer.

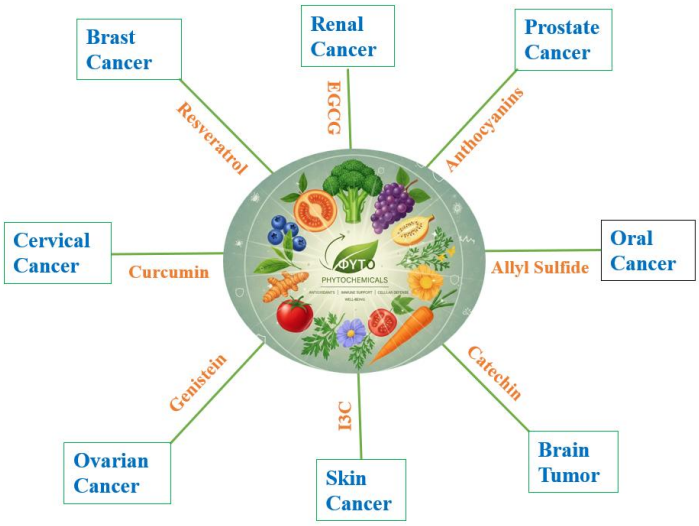


Figure 3. Phytochemicals and Their Anticancer Potential. This infographic illustrates the role of various phytochemicals in preventing and treating different types of cancer. Each phytochemical, such as curcumin, resveratrol, and EGCG, is linked to specific cancers, demonstrating their potential therapeutic benefits in modern cancer treatment.

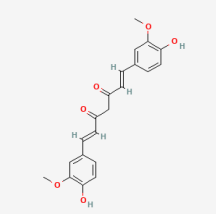
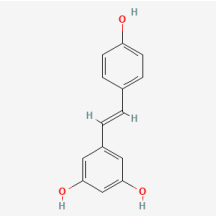
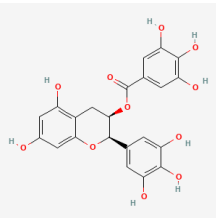
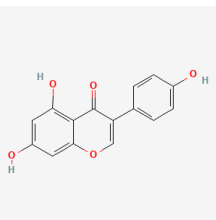
B. Mechanisms of Action of Natural Compounds

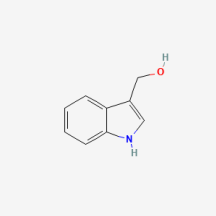
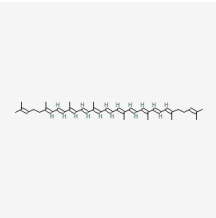
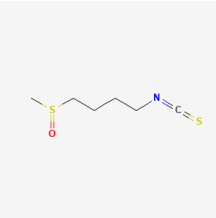
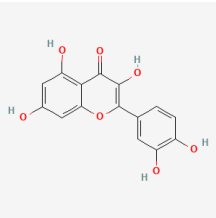
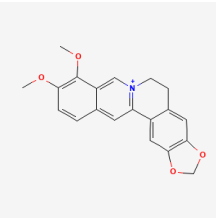
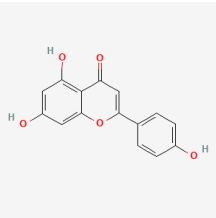
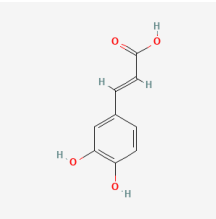
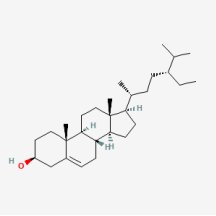
In Table 2, natural compounds have long played an indispensable role in cancer therapy with mechanisms of action that are diverse and plentiful. These compounds also

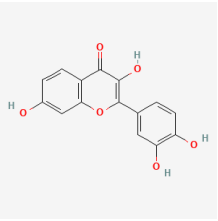
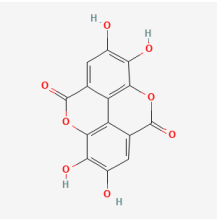
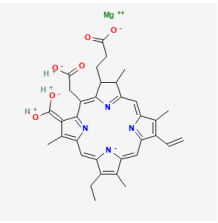
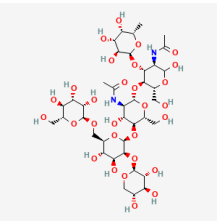
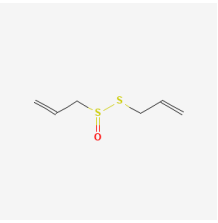
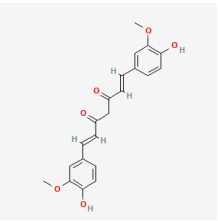
prevent tumor cells from proliferating while promoting apoptosis in these cells. Many phytochemicals such as curcumin, resveratrol and EGCG act against inflammation and oxidative stress that are important components for the evolution of cancer. Curcumin acts mainly through the NF-kB and COX-2 pathways to kill malignant cells by inducing apoptosis and decreasing tumor cell proliferation. Resveratrol and EGCG inhibit the PI3K/Akt and MAPK pathways, thus reducing cancer cell growth inhibiting their metastasis [26], [27].

Natural compounds also boost the body's defenses against cancer. Indole-3-carbinol (I3C) and genistein modulate the estrogen receptor signaling and p53 pathway, promoting DNA repair function and stabilizing tumor cells. Sulforaphane and quercetin stimulate the Nrf2 and NF-kB pathways, processes that play an integral role in detoxification and reducing inflammation which provide increased protection from cancer [28]. These compounds play significant roles as natural and safer alternatives for the discovery of cancer therapies and thus can change future therapy approaches.

Table 2. Mechanisms of Action of Natural Compounds in Cancer Treatment.

Structure of Natural Compounds	Natural Compound	Mechanism of Action	Targeted Cancer Pathways	Key Benefits	Reference
	**Curcumin**	Inhibits inflammation and oxidative stress; induces apoptosis in cancer cells.	NF-kB pathway, COX-2, TNF-α	Reduces tumor growth, enhances immune response, induces cancer cell death.	[27]
	**Resveratrol**	Antioxidant; activates SIRT1 pathway, modulates gene expression related to cell cycle regulation.	PI3K/Akt pathway, SIRT1, p53	Inhibits metastasis, enhances DNA repair, induces apoptosis in cancer cells.	[29]
	**EGCG (Epigallocatechin gallate)**	Inhibits angiogenesis and induces cell cycle arrest.	MAPK/ERK pathway, AKT pathway	Suppresses tumor growth and metastasis, inhibits new blood vessel formation.	[30]
	**Genistein**	Acts as a tyrosine kinase inhibitor, blocking cell cycle progression.	Estrogen receptor (ER), MAPK/ERK pathway	Inhibits cancer cell proliferation, modulates hormone receptor signaling.	[31]

	**I3C (Indole-3-carbinol)**	Modulates gene expression related to detoxification and tumor suppression.	Estrogen receptor signaling, p53, ARF	Regulates estrogen metabolism, inhibits tumor formation, promotes detoxification.	[32]
	**Lycopene**	Antioxidant; induces apoptosis, inhibits proliferation.	PI3K/Akt pathway, MAPK/ERK	Reduces oxidative damage, enhances apoptosis, inhibits tumor cell growth.	[33]
	**Sulforaphane**	Inhibits histone deacetylases and activates antioxidant response elements.	Nrf2 pathway, p53	Promotes detoxification, inhibits cancer progression, enhances tumor suppression.	[24]
	**Quercetin**	Antioxidant; inhibits cell proliferation, enhances apoptosis.	PI3K/Akt pathway, MAPK pathway	Inhibits metastasis, reduces inflammation, induces cancer cell death.	[27]
	**Berberine**	Inhibits cell cycle progression and angiogenesis.	AMPK pathway, PI3K/Akt pathway	Suppresses tumor growth, induces apoptosis, reduces angiogenesis.	[24]
	**Apigenin**	Inhibits histone deacetylase and modulates multiple cancer-related pathways.	p53 pathway, MAPK/ERK pathway	Reduces cancer cell migration, enhances apoptosis, inhibits metastasis.	[34]
	**Caffeic Acid**	Inhibits NF-kB signaling, prevents inflammation, and promotes apoptosis.	NF-kB pathway, MAPK pathway	Suppresses tumor growth, prevents metastasis, reduces inflammation.	[35]
	**Beta-Sitosterol**	Induces apoptosis and inhibits cancer cell proliferation.	MAPK pathway, p53	Inhibits cell proliferation, induces cancer cell death.	[36]

	**Fisetin**	Antioxidant and anti-inflammatory properties that inhibit cancer cell growth.	PI3K/Akt pathway, MAPK pathway	Inhibits metastasis, promotes apoptosis, reduces inflammation.	[37]
	**Ellagic Acid**	Induces apoptosis; inhibits angiogenesis and metastasis.	NF-kB pathway, MAPK/ERK	Prevents tumor growth, inhibits metastasis, enhances cancer cell death.	[35]
	**Chlorophyllin**	Inhibits DNA damage and reduces mutagenesis.	p53, Nrf2	Detoxifies the body, reduces cancer-causing DNA damage.	[25]
	**Bromelain**	Stimulates immune response, enhances the effectiveness of chemotherapy.	NF-kB pathway, p53	Enhances immune system activity, supports chemotherapy effectiveness.	[33]
	**Garlic (Allicin)**	Inhibits cell cycle progression, induces apoptosis, and inhibits metastasis.	MAPK pathway, PI3K/Akt	Reduces oxidative stress, enhances apoptosis, prevents metastasis.	[24]
	**Turmeric (Curcuminoids)**	Blocks inflammation pathways, induces apoptosis, and inhibits angiogenesis.	NF-kB, COX-2	Anti-inflammatory effects, inhibits tumor growth and metastasis.	[13]

C. Challenges in Translating Natural Products

Natural products hold great potential, but translating them into effective treatments for cancer faces numerous hurdles. The first reason is that extracting and purifying active compounds from natural sources is a complicated, lengthy, and expensive process. Because these compounds come from natural sources it can be hard to standardize their quantity and quality so the product is consistent and works as expected [10].

The second issue is that many natural compounds are biologically unstable and can degrade, making them difficult to administer in timely fashion so a nanocarrier needs to address this issue. Formulating these compounds into stable and efficacious products, especially for human application, is still a major challenge. Finally, natural compounds exhibit multiple mechanisms of action to target various cellular pathways, potentially

complicating their dosing and usage [38]. This may lead to the results of clinical trials being inconclusive and the safety and efficacy of natural products remaining, in some instances, unverified.

In addition, many natural compounds are toxic when misused or overdosed, especially if they have not been properly processed. As there is limited research on some plant-based compounds, the side effects and long-term outcomes may be uncertain — this suggests potential risk to health. Higher research efforts, effective quality assurance methods and precise distribution systems are however required to address these limitations. These preventive steps would deliver the efficacy and safety of natural products like methanol anything in for a better option to treat cancer [5], [7].

D. Integration of Natural Products with Modern Drug Discovery

This study further demonstrates the potential integration of natural products with modern drug discovery approaches to enhance their ability to provide novel agents for fighting cancer and other diseases. Natural compounds like curcumin, resveratrol, and EGCG have demonstrated anticancer effects through the suppression of numerous cellular signaling pathways associated with cancer cell growth, survival, and metastasis. Now, we have modern methods for drug discovery, such as computational drug design, nanotechnology, bioinformatics, and genetic engineering, for improving the therapeutic properties of these natural compounds [39], [40]. For example, in order to enhance the efficacy and safety of natural compounds for clinical use, we will combine selective advantages from both natural and synthesized approaches (Table 3).

Scientific study of these compounds commences; we elucidate the mechanism of action of many and understand what can potentially be their targets. This is how natural products integrate with modern drug discovery [41]. Molecular screening techniques and computational modeling of natural products with biological targets have emerged as a powerful tool to enhance their therapeutic efficacy. To improve the bioavailability of these substances and ensure that they reach the main target places, such as cancer cells, nano drug delivery systems can be a big help because of the increasing popularity of nanotechnology. The use of natural compounds in conjunction with modern technologies may yield more effective, safer, and targeted cancer treatments in the future [36].

Table 3. Integration of Natural Products with Modern Drug Discovery.

Integration Aspect	Approach/Technology	Benefits	Reference
Computational Drug Design	Molecular docking, computational modeling	Optimizes the efficacy of natural compounds by predicting their interaction with biological targets and reducing potential side effects.	[42]

Nanotechnology	Nano drug delivery systems	Enhances bioavailability, ensures precise delivery of natural compounds to targeted cancer cells, and improves therapeutic outcomes.	[43]
Bioinformatics	Data analysis, pathway mapping, gene-targeting	Identifies key cancer pathways and provides a detailed understanding of how natural compounds influence molecular processes, facilitating targeted therapy.	[42]
Genetic Engineering	Genetic modifications for enhanced production	Increases the production of bioactive natural compounds, making them more accessible for clinical use while maintaining high quality.	[44]
Combination Therapies	Natural + Synthetic drug combination	Enhances the therapeutic efficacy and minimizes side effects by combining the benefits of natural products with conventional synthetic drugs.	[45]

Synergies Between Computational Drug Design and Natural Therapeutics

A. Computational Screening of Natural Compounds

The approach of the computational screening natural compounds is systematic, where modern technologies are employed at various intervals starting from identification and analysis of plants to target identification [46]. It starts with ethnopharmacological methods and traditional medicine-based approaches to identify plants followed by research studies on their medicinal uses. The authentication and extraction process follows to obtain a pure plant extract (Figure 4).

The extract is screened biologically to assess its therapeutic potential. Then, pure compounds (pure compounds) are isolated from the extract. Following isolation, the pure compounds are characterized with respect to their activity, cellular targets and toxicity through computational modeling and in-silico screening. By identifying whether small natural molecules impact tumor cells through this screening process, we can develop new and potentially more effective drug candidates[5], [47]. During the latter phases,

molecular modeling and structural modification of natural compounds used to design novel analogues with improved activity [37]. Therefore, the incorporation of natural products into contemporary therapeutic systems is more efficient and safer.

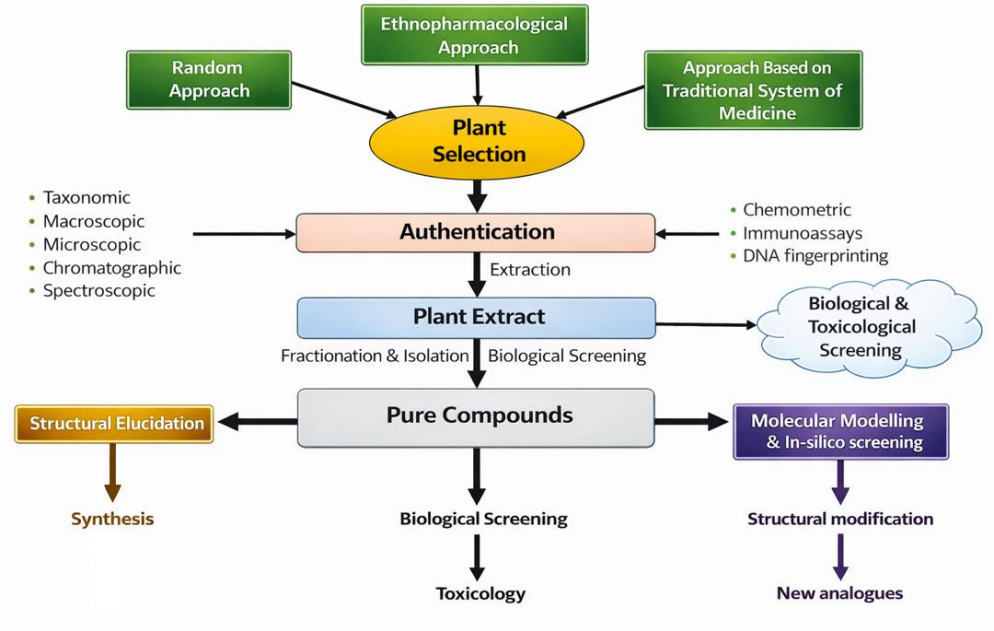


Figure 4. Flowchart illustrating the process of computational screening of natural compounds, from plant selection to the optimization of compounds for preclinical testing.

B. In Silico Modeling of Natural Products

In silico modeling approaches are instrumental in identifying and developing natural products as therapeutic candidates (Table 4). It refers to the use of computer models to simulate predictions about how naturally occurring molecules interact with biological vicinities like receptors or proteins. Working computationally this way lets researchers prioritize natural compounds for lab testing, greatly minimizing time and expense when eliminating unpromising candidates [48].

In silico modeling methods allow the analysis of binding affinity, stability, and potential activity based on various interactions reported for natural products through different techniques (e.g., molecular docking, molecular dynamics simulations, QSAR-model) [16], [49]. Evaluating cell signaling pathways by such methods gives leading factors of the natural drug-induced cytotoxicity; thus, describing mechanism of action [50].

In silico modeling has the major advantage of screening large libraries of natural compounds (e.g., plant-derived phytochemicals) to be evaluated as possible drug candidates. Further, before going into in vitro or in vivo testing, this aids the optimization of these molecules. The drug discovery approach from the nature represents a potential tool to accelerate novel therapies development especially in the fields of cancer, infectious diseases and chronic conditions through an integration of in silico modeling with experimental research [51], [52].

Table 4. In Silico Modeling of Natural Products in Drug Discovery.

In Silico Method	Description	Application in Natural Product Screening	Example Natural Compounds	Advantages	Limitations	Reference
Molecular Docking	A computational technique that simulates the interaction between natural compounds and biological targets.	Identifies binding affinity between natural compounds and target proteins.	Curcumin, Resveratrol, EGCG	Fast screening of large compound libraries; predictive accuracy in target binding.	Can be limited by the availability of accurate protein structures.	[52]
Molecular Dynamics (MD) Simulations	Simulates the physical movements of atoms and molecules over time to study their behavior in dynamic environments.	Analyzes the stability and conformation of natural compounds within biological systems.	Curcumin, Genistein, Lycopene	Provides insights into the compound's behavior in a realistic biological environment.	Computationally intensive and time-consuming.	[53]
Quantitative Structure-Activity Relationship (QSAR)	A method that correlates chemical structure with biological activity to predict the efficacy of compounds.	Predicts the biological activity of natural compounds based on their chemical properties.	Flavonoids, Alkaloids	Can predict the activity of novel compounds; useful for optimization.	Requires extensive data for model development.	[54]
Pharmacophore Modeling	Identifies the essential features of a molecule required to interact with a specific biological target.	Helps in identifying key functional groups in natural compounds that interact with disease targets.	Quercetin, Berberine, Sulforaphane	Identifies critical features of active compounds; simplifies compound design.	May not account for the full complexity of molecular interactions.	[50]
Virtual Screening	A method to screen large compound databases to identify potential drug candidates	Efficiently screens vast libraries of natural products for potential	Resveratrol, Epicatechin, I3C	Increases the efficiency of identifying lead compounds	Can miss compounds with weak binding affinities or non-	[55]

	using computational models.	therapeutic activity.		from large databases.	traditional mechanisms.	
Docking-Based ADMET Prediction	Predicts the Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties of compounds based on docking studies.	Evaluates the pharmacokinetic and safety profile of natural compounds before clinical trials.	Curcumin, EGCG, Genistein	Helps identify compounds with better bioavailability and lower toxicity.	Requires accurate models and can underestimate real-life biological complexities.	[56]

Emerging Trends and Future Directions in Drug Discovery

The process of drug discovery is being radically changed, with Artificial Intelligence (AI) and Machine Learning (ML) techniques increasing efficiency, accuracy, and speed significantly. The application of AI and ML technologies in predicting activity of natural compounds, identifying favorable drug targets and therapeutic screening for vast libraries of compounds is at global large. With access to large datasets and advanced algorithms, AI/ML can improve the drug design process—identifying promising candidate drugs more quickly, which in turn can help minimize the cost and time of drug discovery compared to conventional methods [57], [58]. The application of AI and ML to drug discovery is poised to accelerate the creation of novel therapies, particularly in therapeutic areas like cancer, infectious diseases, and chronic conditions -- potentially allowing researchers to develop more efficacious and tailored treatments.

Drug discovery in modern era is being shaped by Pharmacogenomics and personalized medicine, achieving this comes down to tailoring drugs to suit an individual genetic profile. Pharmacogenomics uses knowledge about genetic variations to predict how a patient's body will respond to specific drugs, leading to the development of better and safer therapies. By choosing the most suitable drug and dosage for an individual, this method reduces adverse drug reactions while improving therapeutic outcomes [59], [60], [61]. Natural products, as well as synthetic drugs, have substantial potential in personalized medicine by facilitating more of a target-based treatment methods that are aligned with the genetic makeup of a patient, leading to higher overall efficacy.

Over the past two decades, advances in structural biology and high-throughput screening (HTS) technologies have greatly expedited the drug-development process. This knowledge combined gives us profound insights into the three-dimensional structures of proteins and how drugs bind to their targets, something that approaches one of the biggest assets offered by structural biology [62]. High-throughput screening allows for the screening of thousands of compounds, including natural products, against a defined

biological target. We can now use this hybrid method of structural biology and HTS to not only rapidly identify potential drug candidates, but also more accurately focus on optimizing compound efficacy [31]. Such technological progress is essential in designing more efficient and selective therapeutics, particularly when extracting natural products using modern drug discovery approaches to provide potent and safer medicines.

CONCLUSION

Fundamental Finding : The integration of natural products with modern drug discovery technologies—such as computational drug design, high-throughput screening, and personalized medicine—demonstrates strong potential for treating various diseases, including cancer, through more efficient identification, optimization, and targeted delivery of bioactive compounds. **Implication :** These advancements contribute to improved efficacy and safety of natural product-based therapies, particularly through innovations in nanotechnology and advanced drug delivery systems that enhance therapeutic performance. **Limitation :** Despite their potential, challenges such as poor bioavailability and toxicity remain significant barriers that limit the optimal application of natural products in clinical settings. **Future Research :** Future studies should emphasize deeper technological integration and continued exploration to enable the development of innovative, effective, and personalized therapeutic strategies based on natural products.

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