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Computational Discovery of Plant Bioactive Compounds Targeting Cancer Signaling Pathways

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ABSTRACT: Cancer is still one of the major causes of morbidity and mortality around the world, and there is a need for safe and effective therapeutic approaches. The application of plant-derived bioactive compounds has gained considerable interest because these compounds are structurally diverse, have pharmacological properties, and can modulate various signaling pathways associated with cancer. The present review summarizes concisely the use of computational methods for the discovery of phytochemicals that hit important onco-signaling pathways, including PI3K/Akt/mTOR, MAPK/ERK, Wnt/β-catenin, NF-κB, JAK/STAT, and p53. The importance of major computational techniques, such as database mining, virtual screening, molecular docking, molecular dynamics simulation, binding free-energy calculation, ADMET prediction, network pharmacology, machine learning, and artificial intelligence, is discussed as a powerful set of techniques to speed up the plant-based drug discovery process. In representative computational studies, the phytochemicals curcumin, quercetin, resveratrol, epigallocatechin gallate (EGCG), berberine, luteolin, withaferin A, and genistein can be multi-target anticancer agents. The review also sheds light on some challenges, prospects, and the integration of computational approaches with experimental validation for the development of safe, effective, and precision-based plant-derived anticancer therapeutics.

1. INTRODUCTION

Cancer is one of the leading causes of death worldwide and continues to impose a substantial health, social, and economic burden despite remarkable progress in diagnosis and treatment. Conventional therapeutic strategies, including surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, have significantly improved survival outcomes; however, their long-term effectiveness is frequently compromised by drug resistance, severe systemic toxicity, tumor recurrence, limited selectivity, and high treatment costs (1). These challenges have intensified the search for safer, more effective, and multi-targeted therapeutic agents capable of overcoming the complexity of cancer biology. Medicinal plants have historically served as an invaluable source of bioactive molecules with diverse chemical structures and pharmacological activities, making them an important foundation for anticancer drug discovery (2). Plant-derived phytochemicals, including alkaloids, flavonoids, terpenoids, polyphenols, lignans, and saponins, exhibit antioxidant, anti-inflammatory, antiproliferative, pro-apoptotic, anti-angiogenic, and anti-metastatic properties by regulating multiple molecular targets and signaling pathways involved in cancer progression (2,3). The successful clinical development of plant-derived anticancer drugs such as paclitaxel, vincristine, vinblastine, and camptothecin derivatives further demonstrates the therapeutic potential of natural products in oncology and supports continued exploration of medicinal plants for novel lead compounds (3). In recent years, computational technologies have transformed phytopharmaceutical research by providing rapid, cost-effective, and reliable approaches for identifying promising anticancer candidates from large phytochemical libraries. Modern computer-aided drug discovery combines virtual screening, molecular docking, molecular dynamics simulations, quantitative structure–activity relationship (QSAR) analysis, network pharmacology, artificial intelligence, and ADMET prediction to evaluate compound–target interactions, predict pharmacokinetic behavior, and optimize lead molecules before laboratory validation (4). These in silico strategies substantially reduce the time, cost, and experimental workload associated with conventional drug discovery while improving the efficiency of identifying plant bioactive compounds that modulate critical cancer signaling pathways such as PI3K/Akt/mTOR, MAPK/ERK, NF-κB, JAK/STAT, Wnt/β-catenin, and p53 signaling (5). Consequently, the integration of computational approaches with natural product research is accelerating the discovery of next-generation plant-derived anticancer therapeutics and advancing precision oncology through mechanism-based drug development (1).

2. PLANT-DERIVED BIOACTIVE COMPOUNDS AS ANTICANCER AGENTS

Plant-derived bio-active compounds have a high structural diversity, biological tolerance, and the ability to specifically target several molecular targets that are associated with the development of tumors, making them one of the most promising sources for novel anti-cancer agents. The medicinal plants are a source of many different secondary metabolites such as flavonoids, terpenoids, phenolic acids, lignans, coumarins, tannins, saponins, glycosides, and organosulfur compounds, many of which have shown potent anticancer activity by various but complementary mechanisms (6). The phytochemicals in them can inhibit uncontrolled cell proliferation, induce apoptosis, promote autophagy, inhibit angiogenesis, prevent metastasis, decrease oxidative stress, modulate inflammatory responses, and regulate immune function, thus interfering with various stages of carcinogenesis (7). Plants have bioactive compounds that act at the molecular level to modulate important pathways involved in cancer, such as PI3K/Akt/mTOR, MAPK/ERK, NF-kB, Wnt/β-catenin, JAK/STAT, p53, and transforming growth factor-β (TGF-β), which subsequently restore normal cellular homeostasis and make it more susceptible to conventional anti-cancer therapies (8). Natural products are playing an important role in modern oncology, and many have been transferred from traditional medicine to clinical use. Taxus species are a source of paclitaxel that interferes with the dynamics of microtubules and is therefore a valuable compound for the treatment of breast, ovarian, and lung cancers; Vincristine and vinblastine, extracted from Catharanthus roseus, are known inhibitors of the formation of the spindle and are widely used in the treatment of hematological malignancies and solid tumors (9). Similarly, camptothecin derivatives, like irinotecan and topotecan, are topoisomerase I inhibitors, and they are now widely used chemotherapeutic drugs for the treatment of colorectal, ovarian, and lung cancers. In addition, however, naturally occurring phytochemicals like curcumin, quercetin, resveratrol, epigallocatechin gallate (EGCG), berberine, genistein, and withaferin A have been found to have high anticancer activity in computer-based and preclinical studies with relatively low toxicity (10). The combination of these bioactive compounds and computational drug discovery has also expedited the discovery of novel phytochemical candidates, which hold new promise for the development of multi-targeted, precision-based, and effective anticancer drugs.

3. MAJOR CANCER SIGNALING PATHWAYS

The dysregulation of several interconnected signaling pathways involved in cellular proliferation, survival, differentiation, metabolism, apoptosis, angiogenesis, invasion, and metastasis contributes to the development and progression of cancer. Of these, the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway is one of the most common oncogenic pathways, contributing to the growth of cells, protein synthesis, metabolic remodeling, and apoptosis resistance in many different types of cancer (11). The mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway is continuously activated in the initiation and progression of tumors and is another important pathway to transmit extracellular growth signals to the inside of the cell that control cell proliferation, differentiation, migration, and survival (12). Likewise, hyperactive Wnt/β-catenin signals promote the retention of cancer stem cells, EMT, metastasis, and drug resistance, as shown by increased levels of β-catenin in the nucleus and upregulation of oncogenic pathways (13). Nuclear factor-kappa B (NF-ϰB) pathway is central to the processes of cell survival and proliferation, immune evasion and the production of inflammatory cytokines, and has been central to chronic inflammation-associated carcinogenesis, while Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is activated in a constitutively active manner, which has been important in the processes of malignant transformation, immune suppression, tumor growth and metastatic progression (14).The tumor suppressor p53 signaling pathway is activated to repair the cellular genome, halt the cell cycle, or induce senescence/apoptosis in response to cellular stresses, and genomic mutations or inactivation of p53 is one of the most frequently observed molecular changes in human cancers. In addition, changes in the proteins involved in apoptosis regulation (e.g., Bcl-2 family proteins, caspase cascades) and alterations in the regulation of the cell cycle (e.g., dysregulation of cyclins and cyclin-dependent kinases [CDKs] and cell cycle checkpoints) play a role in the development of unchecked proliferation and resistance to programmed cell death (15). Figure 1 illustrates the way these signaling pathways are intricately interconnected with each other, and that plant-based bioactive extracts such as curcumin, quercetin, resveratrol, berberine, epigallocatechin gallate, and withaferin A can target several molecular targets simultaneously, providing a robust mechanistic foundation for computational-aided discovery of phytopharmaceuticals and precision anticancer drugs.

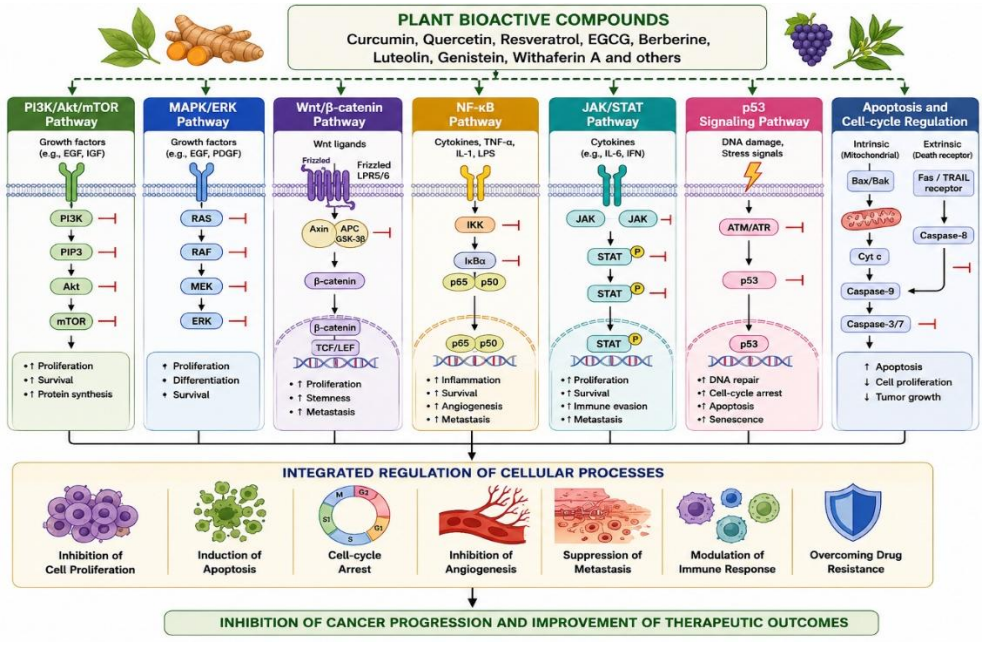

Figure 1. Overview of Major Cancer Signaling Pathways Targeted by Plant Bioactive Compounds

4. COMPUTATIONAL APPROACHES IN PLANT-BASED DRUG DISCOVERY

The "revolutionary" computational techniques can develop strategies for the identification of bioactive phytochemicals with anticancer activity in the short term using high throughput and cost-effective methods. The process is typically initiated by a search of natural products databases, including PubChem, ChEMBL, IMPPAT, NPASS and COCONUT for information and data on the chemical structure, physicochemical properties, biological activities and pharmacological profile of plant compounds

that might be investigated as potential therapeutic molecules and then screened in huge amounts of thousands of compounds (16). After the database mining, the preparation of the ligands, identification of the target, optimisation of 3D molecular structure, assignment of protonation states, energy minimization and identification of disease-associated protein targets involved in cancer signalling pathways like PI3K, Akt, mTOR, EGFR, BRAF, STAT3, NF-κB and β-catenin (17) are performed. The binding orientation, binding interaction and binding affinity of the phytochemicals to the target proteins are then predicted by molecular docking to select the phytochemicals with high inhibitory potential (18). In addition, molecular dynamics simulation is performed to validate the docking results, used to study the stability of a protein–ligand complex, conformational flexibility and the behaviour of the complex in the physiological conditions, providing insight into the stability of interaction during time (19). Binding free-energy calculations like Molecular Mechanics/Poisson–Boltzmann Surface Area (MM/PBSA) and Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) help to quantitatively estimate the strength of molecular interactions and increase the reliability of lead compound selection (20).In addition, absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction is widely used for the evaluation of pharmacokinetic properties and safety profile in early stages, thus decreasing the risk of a drug failure in later stages (21). With the multi-component and multi-target property of medicinal plants, network pharmacology is also a good complement to phytopharmaceutical research, which can elucidate the complex interaction among phytochemicals, multiple molecular targets, signaling pathways, and disease networks. In recent years, machine learning and artificial intelligence have also become revolutionary technologies that can predict biological activity, identify new drug targets, optimize the lead compounds, analyze omics data at scale, and speed up decision making across the drug discovery process, offering a significant boost to the efficiency and accuracy of computational phytopharmaceutical research (23).

5. COMPUTATIONAL WORKFLOW FOR PLANT BIOACTIVE COMPOUND DISCOVERY

computational workflow for plant bioactive compound discovery towards cancer signaling pathways is an integration of a number of in silico methods aimed at the acceleration of discovery, optimization and validation of potential therapeutic candidates, thus reducing the time and cost of conventional drug discovery. The first step is the mining of the database, where the chemical structure, biological activity and physicochemical properties (24) of the phytochemicals are taken from databases of natural products, which are publicly available, like PubChem, ChEMBL, IMPPAT, NPASS, COCONUT, and ZINC. Compounds collected are then subjected to a rapid analysis of huge phytochemical libraries using virtual screening against several selected protein targets relevant to cancer to identify compounds that have a good binding affinity and drug-like properties (25). The candidates selected are then bound to the key proteins involved in oncogenic pathways such as PI3K, Akt, mTOR, EGFR, STAT3, NF-κB and β-catenin (26) and studied with respect to the direction of binding, interaction pattern, binding affinity.

The docking results are validated using the Molecular dynamics (MD) simulation, the stability, flexibility, and conformational behaviour of the molecular interactions between the protein and the ligand under physiological conditions are studied, and the temporal dynamic information of the molecular interactions is obtained (27). This is followed by an assessment of the absorption, distribution, metabolism, and excretion (ADMET) properties of promising phytochemicals in terms of their absorption and distribution in the body, metabolism, excretion, and toxicity, to identify those with poor ADMET properties early on during the drug development process, thereby reducing the probability of their development (28). The last step is biological validation using in vitro cell-based assays, enzyme inhibition assays, mechanistic studies, and in vivo animal models to validate the anticancer activity, mechanism of action, and therapeutic potential of the prioritized compounds. The integrated computational pipeline is depicted in Figure 2 and involves a systematic approach to target plant-derived bioactive compounds to modulate important cancer signaling pathways efficiently, which is achieved through the following steps: database mining, virtual screening, molecular docking, molecular dynamics simulation, ADMET assessment, and experimental validation. The advanced computational techniques, along with biological validation, ensure reliability, efficiency, and translatability in phytopharmaceutical research for developing safe, effective, and precision-based plant-derived anticancer therapeutics (29).

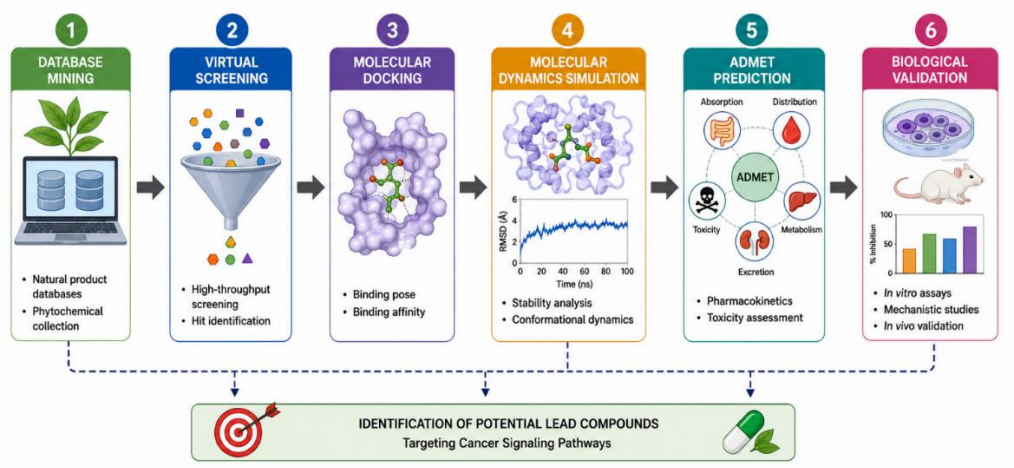

Figure 2. Computational Pipeline for Discovery of Plant Bioactive Compounds Targeting Cancer Signaling Pathways

6. REPRESENTATIVE COMPUTATIONAL STUDIES

To illustrate these compounds' vast potential as multitarget anticancer agents, representative computational studies are used that demonstrate that plant derived bioactive compounds interact with a number of important proteins involved in cancer initiation and progression. The curcuminoid curcumin is the main polyphenol compound of Curcuma longa and has been extensively studied for its binding affinity with PI3K, Akt, mTOR, NF-ϰB and STAT3, which show strong binding affinity and inhibit the growth of tumors and induce apoptosis (25). Quercetin is a natural occurring flavonoid that has been shown to have interesting interaction with several signaling proteins such as the EGFR, PI3K, MAPK and β-catenin, which suggests inhibition of cell proliferation, angiogenesis and metastasis (26). In similar fashion, the stilbene polyphenol found in grapes and berries, resveratrol, was found to also bind NF-ϰB, STAT3, and p53 as well as other oncogenic targets, thereby supporting its anti-inflammatory, antiproliferative, and pro-apoptotic effects across multiple cancer types (27). The primary catechin in green tea, epigallocatechin gallate (EGCG), was computed as a potent inhibitor of the VEGFR, EGFR, PI3K, and MAPK signaling proteins, indicating that green tea could have potent anti-angiogenic and anticancer properties (28). Berberine, an isoquinoline alkaloid from Berberis species, was shown to interact with Akt, mTOR, AMPK, and NF-ϰB proteins without changing their stability and is a strong inhibitor of the survival and migration of cancer cells (29). The study of flavone suggests that luteolin has high docking affinity with ERK and JNK, cyclin-dependent kinases, and PI3K, and induces apoptosis and cell cycle arrest (30). Likewise, Withaferin A, a steroidal lactone extracted from Withania somnifera, was shown to have a good binding to NF-ϰB, STAT3, Hsp90 and vimentin, suggesting that it has anti-inflammatory, anti-Epithelial–mesenchymal transition (anti-EMT) and anti-tumor metastasis effects (31). Furthermore, genistein is an isoflavone compound of soya beans that is known to have strong interactions with tyrosine kinases, estrogen receptors, and the Wnt/β-catenin signaling pathway and therefore exerts inhibitory effects on cell proliferation and pro-apoptotic effects in various cancer models (32). To conclude, these computational studies illustrate the potential of plant bioactive compounds to simultaneously target multiple targets associated with cancer and provide a solid scientific foundation for new, safe, and effective phytopharmaceuticals for precision cancer therapy.

7. ADVANTAGES AND CHALLENGES

The combination of computational approaches has revolutionized the field of plant-based anticancer drug discovery, allowing for the screening of huge drug libraries in seconds, the prediction of targets with high accuracy, the cost reduction of research, and the identification of promising lead compounds before starting experimental research (33). They improve the efficiency of the drug discovery process with the help of molecular docking, molecular dynamics simulation and ADMET prediction, and help multi-target drug discovery. However, there are numerous problems to be addressed including problems with data quality, lack of standard phytochemical databases, and biological annotations that are incomplete and differ between computational algorithms. Furthermore, the multi-target effects of phytochemicals are a large hurdle to predict therapeutic effects and to make them available for clinical use, and in silico predictions should be validated by a comprehensive experimental and clinical validation (34).

8. FUTURE PERSPECTIVES

Artificial Intelligence (AI), Deep Learning, Multi-omics data, Digital twin technologies, Precision Oncology and Explainable AI will be instrumental in the future of computational anticancer drug discovery. In mere moments and with greater precision, AI and deep learning algorithms can accurately predict bioactive compounds, optimize them into lead molecules, and identify new therapeutic targets. The combination of multi-omics (genomics, transcriptomics, proteomics and metabolomics) will also help to gain insights into the complex cancer biology and mechanism of phytochemicals. Information from these models will be used to make therapeutic simulations that will be patient-specific, and precision oncology will support the individual treatment plans. Explainable AI will increase the model transparency, reliability, and clinical acceptance, which will propel the development of safe, effective, and evidence-based plant-derived anticancer therapeutics.

9. CONCLUSION

The structural diversity of compounds from plants, along with their multi-target therapeutic activity, makes them an important source of new anticancer drugs. The computational methods, such as virtual screening, molecular docking, molecular dynamics simulation, network pharmacology, and AI in drug discovery, have expedited the identification and optimization of promising phytochemicals that target key pathways in cancer. The integrated strategies cut the costs of research, enhance the accuracy of predictions, and target candidates for experimental validation. Precision phytopharmaceuticals will continue to advance with the progress of computational technologies and biological and clinical research, leading to the development of future clinical cancer therapies that will be safer, more effective, and personalized.

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