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Short Communication

Rapid Screening of Natural Compounds for Novel Anticancer Drug Candidates

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DESCRIPTION

The discovery of novel drugs is an inherently time-consuming and resource-intensive process, often taking over a decade from initial compound identification to clinical approval. The high attrition rates in drug development, particularly during the clinical trial phases, underscore the need for more efficient strategies in early-stage drug discovery. Natural compounds, derived from plants, microorganisms, and marine sources, have historically served as a rich reservoir of bioactive molecules due to their remarkable structural diversity and inherent biological activities. Many clinically approved anticancer drugs, including paclitaxel and vincristine, originate from natural sources, highlighting their enduring relevance [1-3].

Recent advances in computational methods, particularly in silico approaches such as molecular docking, virtual screening, and pharmacokinetic prediction, have significantly accelerated the identification of potential therapeutic candidates. These methods allow researchers to rapidly screen large libraries of compounds against specific molecular targets, reducing both the time and cost associated with traditional experimental screening. This study presents preliminary findings from a rapid in silico screening approach aimed at identifying potential anticancer agents from natural compound libraries, focusing on three key oncogenic targets: EGFR, BCL-2, and VEGFR-2, which are implicated in tumor proliferation, survival, and angiogenesis [4-5].

MATERIALS AND METHODS

A curated library of 500 structurally diverse natural compounds, including flavonoids, alkaloids, terpenoids, and polyphenols, was obtained from publicly available chemical databases. Molecular docking studies were conducted using AutoDock Vina to evaluate the binding affinities of these compounds against the ATP-binding sites of EGFR and VEGFR-2, and the BH3-binding groove of BCL-2. Compounds demonstrating high predicted binding affinity (binding energy < -8 kcal/mol) were further analyzed for drug-likeness using Lipinski's Rule of Five. Additional pharmacokinetic and toxicity profiles, including absorption, distribution, metabolism, excretion, and toxicity (ADMET) parameters, were predicted using the SwissADME and pkCSM online tools.

Molecular docking results were visualized and analyzed using PyMOL to examine interactions such as hydrogen bonding, hydrophobic contacts, and π-π stacking. Compounds with favorable docking poses and pharmacokinetic profiles were shortlisted as potential anticancer candidates for further evaluation.

RESULTS AND DISCUSSION

Preliminary in silico screening identified several natural compounds with strong predicted binding affinities for the selected targets. Notably, specific flavonoids and alkaloid derivatives displayed robust interactions with the ATP-binding pockets of EGFR and VEGFR-2, suggesting their potential as kinase inhibitors. One alkaloid compound was predicted to inhibit BCL-2, which may induce apoptosis in cancer cells through the intrinsic apoptotic pathway. Detailed analysis of docking poses revealed that key interactions included hydrogen bonds with critical residues in the active sites and hydrophobic contacts that stabilized ligand binding.

The ADMET analysis indicated that five shortlisted compounds exhibited favorable oral bioavailability, low predicted toxicity, and high gastrointestinal absorption, supporting their potential as drug-like molecules. While these results are purely computational predictions, they provide a rapid and cost-effective means of prioritizing compounds for experimental validation. Integrating such computational tools into early drug discovery workflows enables researchers to focus on the most promising candidates, reducing the reliance on labor-intensive high-throughput screening methods.

Furthermore, the diversity of the identified compounds emphasizes the potential of natural products to serve as scaffolds for novel anticancer drug development. Structural modification and optimization based on these scaffolds could further enhance binding specificity, potency, and pharmacokinetic properties, paving the way for rational drug design strategies.

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In addition to their structural diversity, natural compounds often possess evolutionary-optimized interactions with biological macromolecules, making them particularly valuable starting points in anticancer drug discovery. Unlike many synthetic compounds that are designed in isolation, natural products have co-evolved with biological systems, resulting in unique stereochemistry and functional group arrangements that enable high-affinity interactions with protein targets. This evolutionary advantage underscores why natural products have historically contributed so significantly to the pharmacopeia and why continued exploration of natural compound libraries remains a promising avenue for uncovering novel anticancer agents.

Another important consideration arising from this study is the potential for polypharmacology, where a single natural compound may modulate multiple oncogenic targets simultaneously. Cancer is a multifactorial disease characterized by dysregulation of numerous signaling pathways, and monotherapy directed at a single target often leads to resistance. The observation that several compounds displayed predicted activity across more than one target, such as EGFR and VEGFR-2, highlights their potential to provide multi-targeted therapeutic effects. Such compounds could reduce the likelihood of resistance and improve clinical efficacy, particularly when used in combination with existing chemotherapeutics.

Finally, while computational predictions offer a valuable starting point, it is crucial to acknowledge the limitations of in silico methods. Docking scores and ADMET predictions provide estimates rather than definitive biological outcomes, and experimental validation remains indispensable. Future work will involve biochemical assays to confirm binding interactions, followed by in vitro and in vivo studies to assess anticancer activity and safety profiles. Nevertheless, the workflow established in this study demonstrates the efficiency of combining molecular docking with pharmacokinetic predictions as a front-line strategy in natural product-based drug discovery. By narrowing down large chemical spaces to a small set of highly promising candidates, this approach can significantly streamline the pipeline toward the development of novel anticancer therapeutics.

CONCLUSION

This study demonstrates the value of in silico screening in rapidly identifying potential anticancer agents from natural compound libraries. Five compounds exhibited strong predicted interactions with EGFR, BCL-2, and VEGFR-2, alongside favorable drug-likeness and ADMET profiles, suggesting their suitability for further experimental evaluation. Future work will involve in vitro assays to validate the cytotoxic and apoptotic effects of these compounds, followed by in vivo studies to assess efficacy, pharmacokinetics, and safety profiles. Additionally, structure-activity relationship (SAR) studies and molecular dynamics simulations could refine these compounds, enhancing their therapeutic potential.

The integration of computational screening with experimental validation represents a promising approach to accelerate the drug discovery pipeline, particularly in the search for novel anticancer agents derived from natural sources. This study reinforces the critical role of natural products in modern drug discovery and highlights how computational strategies can efficiently guide the selection of promising candidates for further development.

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