Computer-Aided Drug Design in Anticancer Drugs

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Abstract

The fight against cancer is a significant global health issue, and creating effective anticancer medications is crucial to addressing this challenge. Traditional methods of developing these drugs are time-consuming and require substantial financial investment. However, computer-aided drug design technology can reduce the time and cost associated with research and development. This paper summarizes various studies that have utilized computer-aided drug design technology to create anticancer drugs. It explores the application of this technology in cancer research and serves as a reference for future development of anticancer medications.

Keywords: Anticancer Drugs, Cancer poses, molecular, bendamustine, Ligand-based drug design

Introduction

Cancer poses a severe threat to human health and life. According to the World Health Organization, cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, or one in six deaths, in 2018(WHO, 2023). Among the three major therapies for cancer treatment, drug therapy is one. With the rapid development of science and technology and advancements in molecular oncology and molecular biology technology, new anti-tumor drugs are continually emerging, and research and development in anticancer drugs have entered a new stage. However, as of 2023, most common solid tumors, such as lung cancer and pancreatic cancer, still lack effective drugs, and many antineoplastic drugs have developed resistance during clinical applications, making the need for new antineoplastic drugs imperative. Developing anticancer drugs can enhance patients' survival rate and quality of life, which is significant to maintaining human health and vitality. Traditional anticancer drugs are more toxic, less effective, and more expensive to develop, and many anticancer drugs have resistance problems after long-term use, resulting in the original drugs being unable to continue to work. Thus, there is a need to find a more efficient and cost-effective way of developing anticancer drugs to meet the growing demand for them. By utilizing computer-aided design for anticancer drugs, the success rate of research and development can be improved, the R&D cycle can be shortened, and the R&D cost can be reduced.

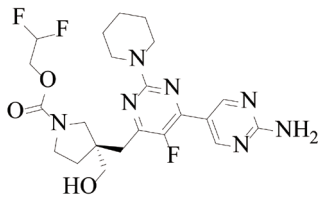
Drug research and development (R&D) has a low success rate, long cycle, high cost, and low efficiency. Computer-aided drug design (CADD) uses computer technology and algorithms to predict and design drug candidates to expedite the drug development process. CADD involves designing and optimizing lead compounds through computer simulations and calculations of interactions between receptors and ligands. This method has been widely used to treat various diseases. With advancements in computer and artificial intelligence technologies, CADD technology will be extensively used in treating Alzheimer's disease(Ambure & Roy, 2017), neurodegenerative disorders(Baig et al., 2018), and cardiovascular disease(Llorach-Pares et al., 2022). CADD applications include structure-based drug design, ligand-based drug design, and virtual screening technologies. This paper examines the research on these three CADD techniques for anticancer drugs.

Structure-based drug design

Structure-based drug design (SBDD) utilizes information obtained from the 3D structure of a molecule, with particular attention to the interactions between the ligand and target. Computer-assisted methods are also employed to discover and optimize lead compounds to enhance the specificity and effectiveness of drug-target binding. SBDD aims to identify ligand molecules that can bind specifically to the receptor, using the receptor's structure and properties as a guide. This type of drug design is also known as direct drug design and includes techniques such as molecular docking based on receptor structure, active site analysis, and novel drug design. Popular software(Kapetanovic, 2008) used for molecular docking includes Autodock, Gold, Dock, Glide, and MOE.

In 2021, Cheng et al. discussed the discovery, design, and synthesis of various compounds as selective inhibitors of phosphatidylinositol 3-kinase (PI3K) alpha isoform. The compounds were optimized for potency, selectivity, and ADME properties through computational analysis, crystal structure determination, and in vitro assays. The most promising compounds showed high potency and selectivity against PI3K alpha, making them potential candidates

for cancer treatment. The synthesis process involved multiple steps and purification techniques. Furthermore, the article does not provide data on the efficacy of PF-06843195 in preclinical or clinical models, which would be valuable information to assess its potential as a cancer treatment. While the research presents promising findings in discovering and synthesizing a selective PI3K α inhibitor, further studies are needed to evaluate its efficacy and address the limitations observed in animal models and drug solubility(Cheng et al., 2021).



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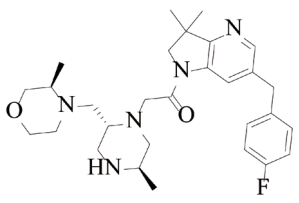
Tamanini discusses the discovery and optimization of a small-molecule antagonist of cellular inhibitor of apoptosis protein 1 (cIAP1) and X-linked inhibitor of apoptosis protein (XIAP). The compound, called AT-IAP, is a potent and orally bioavailable dual antagonist of cIAP1 and XIAP and serves as a novel chemical probe for IAP biology. They used these techniques to efficiently grow into the P2 and P4 pockets of the target protein, XIAP-BIR3. By analyzing the crystal structure of the lead compound bound to XIAP-BIR3, they identified vital interactions and sub-pockets that could be targeted for optimization. Overexpression of these proteins has been associated with tumor progression and resistance to treatment [2]. By targeting and inhibiting XIAP and cIAP1, AT-IAP has the potential to promote apoptosis and overcome resistance to apoptotic stimuli in cancer cells. The authors describe the structure-based drug design approach used to optimize the compound and its potential as a therapeutic target for cancer treatment. The article provides no clinical data on the compound's effectiveness in treating cancer patients. Further research is required to determine its clinical potential. Overall, while the research presents a promising compound with potential in cancer therapeutics, further studies are needed to fully evaluate its efficacy, safety, and clinical potential(Tamanini et al., 2017).



cIAP1

In 2021, this research article presents the development of a supramolecular nanomedicine for breast cancer therapy. The researchers created a D-peptide-small molecule drug conjugate by combining a high-affinity MDM2-targeted D-peptide inhibitor with the chemotherapy drug bendamustine. The conjugate demonstrated strong inhibitory effects on breast cancer cell growth in vitro and significant inhibition of tumor growth in vivo, with no apparent side effects. This study offers a promising approach to developing effective and low-toxicity cancer therapies. The article must provide detailed information on the research data, as it states that the data are not shared.

Additionally, the in vivo toxicological assessment of BEN-FF-peptide 5 is limited to body weight changes, organ indexes, and H&E staining. Further, toxicological studies and a comprehensive evaluation of the nanomedicine's safety profile would be beneficial. Lastly, the article must discuss the potential challenges or limitations of translating the research findings into clinical applications. Further studies and considerations are needed to fully assess these nanomedicines' efficacy, safety, and clinical feasibility(Zhou et al., 2021).

To sum up, SBDD offers benefits such as enhancing binding affinity and improving potency and selectivity against targets. However, it is essential to note some limitations. SBDD requires a comprehensive and distinct three-dimensional structure of the target and only considers the drug-receptor binding strength, which cannot predict the drug's effectiveness. Moreover, it is a slow process(Van Montfort & Workman, 2017).

ligand-based drug design

In Ligand-based drug design (LBDD), the activity of new compounds is predicted, or the existing compounds are structurally improved. This is done by creating pharmacophore models or quantitative conformational relationships from active small molecule structures. Two main methods are used in Ligand-based drug design: pharmacophore model construction and quantitative conformational relationship analysis.

Pharmacophore model construction is an important method for discovering lead compounds and can be established based on ligands or receptors. A ligand-based pharmacophore model begins with the structure of a series of active compounds and identifies the essential elements, such as hydrophobicity and hydrogen bonding, required for their biological activities. On the other hand, the receptor-based pharmacophore model is established by examining the interaction points between biomolecules and ligands. Once the pharmacophore model is established,

3D searching of compounds in the database can help enrich the active compounds, leading to the discovery of new active molecules.

Quantitative conformational relationship analysis is based on homologous molecules with the same parent. It uses mathematical and statistical methods to construct equations, analyze the biological activity of compounds and their structural changes, and predict the activity of modified compounds for lead compound optimization. The structure-effect relationship analysis is divided into 2D-QSAR and 3D-QSAR. Common software for constructing pharmacophores includes HipHop, HypoGen, DISCO, GASP, and PHASE(Yang, 2010).

Researchers explore the potential of fullerene derivatives as inhibitors of lung cancer cells. The authors synthesized water-soluble fullerene derivatives and tested their anti-tumor effects on human lung carcinoma cells. They used quantitative structure-activity relationship (QSAR) modeling to investigate the relationship between the fullerene derivatives' anticancer effects and molecular descriptors. The results showed that certain structural features were positively correlated with the cytotoxicity of the fullerene derivatives against lung cancer cells. The authors suggest that the QSAR model can guide the future rational design of fullerene-based drug candidates for lung cancer therapy.

On the other hand, there are some disadvantages of article research. Some research methods, such as protein active center docking methods, may need to be improved in accurately understanding the mechanisms of action of bioactive compounds. QSAR, while useful in finding potential properties of chemical derivatives, may need help in establishing reasonable models through appropriate properties. Overall, article research provides valuable insights and knowledge in various fields, but it is important to consider the limitations and challenges associated with specific research methods and existing treatments(Huang et al., 2020).

Ganji discusses the discovery of potential fibroblast growth factor receptor 3 (FGFR3) inhibitors in treating bladder cancer. The researchers used pharmacophore and QSAR modeling approaches to identify potential inhibitors for FGFR3 in bladder cancer treatment. They screened the ZINC and NCI databases using these modeling techniques to identify compounds with inhibitory activity against FGFR3. The compounds were further filtered based on factors such as ADMET properties and Lipinski's Rule of Five. The selected compounds were then subjected to flexible docking analysis to analyze their interactions with FGFR3. The selected compounds show promising interactions with FGFR3 and may have effective inhibitory properties. These compounds could be candidates for bladder cancer therapy with improved therapeutic properties and fewer adverse effects(Ganji et al., 2023).

Someone discusses the use of pharmacophore modeling to identify potential inhibitors for the human cytochrome P450 17 enzyme, which is involved in producing androgens and is a target for prostate cancer therapy. The researchers generated pharmacophore models based on known inhibitors and used them to search databases for new compounds. They identified several steroidal compounds with potential inhibitory activity, some of which showed high potency in further testing. The study highlights the potential of pharmacophore modeling in discovering new and potent inhibitors for prostate cancer therapy(Clement et al., 2003).

In 2022, Sharma discussed the use of structure-based pharmacophore modeling, machine learning, and molecular dynamics simulations to identify potential inhibitors for Bruton's tyrosine kinase (BTK), a critical enzyme involved in cancer. The study screened a chemical database using machine learning models and generated a ligand-based pharmacophore model for virtual screening. The top compounds were further analyzed through molecular dynamics simulations and evaluated for their anti-proliferative effects on cancer cell lines. Four compounds showed promising results as BTK inhibitors, demonstrating significant BTK kinase inhibition activity and growth inhibition of cancer cell lines. While the article research employed a comprehensive methodology and utilized advanced computational techniques, some limitations should be considered, such as imbalanced data and lack of validated FEC(Sharma et al., 2022).

To summarize, LBDD uses known ligand structures to design drugs with strong binding ability with the receptor, ultimately enhancing drug efficacy. Designing drugs based on the ligand structure can target specific areas and have a clear mechanism of action, leading to improved drug development efficiency. However, if the ligand structure is unclear or uncertain, it may impact the success rate of drug design(Acharya et al., 2011). It's important to note that this method is limited to designing drugs for known ligand structures and doesn't allow for the discovery of new targets, which restricts the scope of drug design.

Virtual screening

Virtual screening, also known as computer-based screening, is a method that uses computer software to simulate the interaction between a drug candidate and a target. Calculating the affinity between the two can reduce the number of compounds screened, leading to a more efficient discovery of lead compounds. Virtual

screening is based on various information, including known drug molecular structures and biomolecular mechanisms of action. It uses several applications and models to predict molecule interactions, such as pharmacophore search and high-throughput docking. This approach is crucial in new drug discovery, and AI plays a significant role in identifying potential lead compounds. Virtual screening saves time and effort and reduces the number of "invalid trials" in drug development. Popular HTD programs include Gold, Dock, Glide, FlexX, and LigandFit(McInnes, 2007).

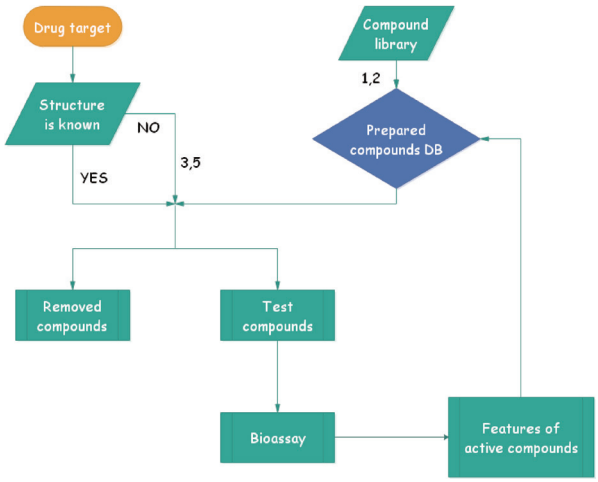


Figure 1 The application of the combination of virtual screening and bioactivity screening. 1: Removal of non-drug compounds; 2: Removal of false positive compounds; 3: Pharmacophore searching; 4: Molecular docking; 5: Molecular similarity

Zhang discusses identifying and characterizing a potential mTOR inhibitor called MT-5 for treating colorectal cancer. The researchers conducted virtual screening and various assays and stated that a rational virtual screening approach was employed to identify structurally novel and potentially active lead compounds. The compounds were screened using shape screening and molecular docking techniques to evaluate the compound's inhibitory activity, stability profiles, and binding to the mTOR protein. The study suggests that MT-5 has promising anticancer activity and could be further developed as a potential therapeutic agent. In the article, Rapalogs are described as having complicated structures, large molecular weights, low productivity, and difficulties in enantiomer separation. These characteristics pose challenges in their development and use as therapeutic agents and have been terminated in clinical evaluation due to poor tolerance and drug resistance. This suggests that further safety and efficacy improvements are needed (Zhang et al., 2023).

Someone discusses the use of virtual screening methods to discover potential inhibitors of ubiquitination regulators for cancer treatment. The articles highlight the importance of ubiquitination in cellular processes and its role in cancer growth and metastasis. By utilizing virtual screening, companies can identify potential inhibitors without consuming valuable materials, and these hits can then be verified using in vitro experiments. They also explore the different enzymes involved in the ubiquitination process and the potential targets for drug inhibition. In the context of ubiquitination regulators, virtual screening has been employed to identify inhibitors of cancer targets, and the articles provide examples of successful studies in this field(Song et al., 2021).

In 2019, Russo Spena identified a potential inhibitor called VS10 for the protein PIN1, which is overexpressed in high-grade serous ovarian cancer. The researchers used virtual screening and molecular dynamic simulations to identify VS10 as an inhibitor of PIN1 isomerization. Further testing showed that VS10 reduced the viability of ovarian cancer cell lines, induced PIN1 degradation, and decreased PIN1 downstream targets. These findings suggest that VS10 could be a potential therapeutic agent for PIN1-overexpressing tumors (Russo Spena et al., 2019).

Drug discovery and design have a new method called virtual screening that boasts high efficiency, speed, and cost-effectiveness. The technology is employed to identify the targets of existing drugs and explain how they work. Its application in drug development and other fields is ongoing. With further advancements in science and technology, virtual screening will undoubtedly play a major role in the future of drug development. However, there are limitations to its use, such as the lack of protein crystal structure determination, which restricts the potential of molecular docking.

Conclusion

This document summarizes various studies on how computer-assisted techniques can aid in developing anticancer drugs. The research indicates that computer technology is beneficial for designing and optimizing these drugs. Computer-assisted drug technology is becoming increasingly prevalent in drug design and development.

After reviewing the literature, it was discovered that computer-assisted drug design necessitates significant data support and ongoing algorithm optimization. This, in turn, requires high computational resources, extensive

knowledge of medicinal chemistry and biology, and a thorough understanding of computational biology and systems biology, among other fields. These factors all contribute to the difficulty of computer-assisted drug design. However, new and improved concepts of computer drug design continue to emerge, and the corresponding procedures and algorithms must follow suit. The development of personalized medicine requires the advancement of basic life science disciplines and the integration and penetration of biological and medical data. Computer-assisted drug design has many applications in the drug design field, and virtual screening is expected to play an increasingly important role in drug development as computer technology and artificial intelligence continue to improve.

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