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"Computer Aided Drug Design On Anti Cancer Drugs"

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I. Introduction:

Cancer is a complex disease that can arise from many different causes, and its progression and spread are influenced by multiple factors. The interactions between hereditary and environmental factors can lead to the transformation of normal cells into tumor cells, which can then grow and invade surrounding tissues and spread to other organs [1]. The incidence of cancer varies widely across different regions of the world, reflecting differences in lifestyle, environmental factors, and access to healthcare. The burden of cancer is expected to continue to rise in the coming years, highlighting the importance of developing new effective treatments to help reduce the impact of this disease .

Over the course of time, many treatment methods, such as radiation and chemotherapy have been developed to combat cancer prevalence. These therapies have been effective in the treatment of some cancers, but these treatment options have limitations, such as low efficacy, toxicity, and resistance to drugs. In addition, many cancer treatments are not well-suited to the individual needs of each patient, leading to suboptimal outcomes [4]. The development of resistance to current cancer treatments is a growing concern. This resistance is driven by the ability of cancer cells to evolve and develop resistance to chemotherapy. Hence, new treatments that target different pathways and uses different mechanism of action are needed to overcome drug resistance.

In the past few years, numerous therapeutic targets have been identified, which has offered innovative approaches for preventing tumorigenesis and reducing tumor burden [5]. To provide effective therapies for cancer patients, traditional drug discovery has been used to design and develop drugs that can eradicate cancer cells with minimal harm to healthy cells. This process involves the identification of targets, chemical synthesis of compounds, preclinical testing *in vitro* and animal models and toxicity assessment. Successful compounds are then subjected to clinical trials in humans to evaluate their safety and effectiveness in the target patient population, which can take several years to complete [6]. Despite the success of this approach in developing effective anticancer drugs, it is a time-consuming, laborious, and expensive process that can take many years and millions of dollars to complete. Therefore, recent advancements in technology and techniques have led to the development of computational methods which have been used to expedite and simplify the discovery of novel anticancer drugs.

Computer-Aided Drug Discovery And Design:

Since the advent of the X-ray diffraction to unveil the chemical composition and three-dimensional (3D) geometry of a small organic molecule in 1932,[7] a large number of proteins have been solved either by X-ray or by nuclear magnetic resonance (NMR) spectroscopy and are available at open access protein databases (http://www.rcsb.org). This information allows researchers to understand and characterize many physiological processes based on interactions between proteins or between proteins and small molecules (ligands), as the case of the drug-target binding.

In 1962, Max Perutz and John Kendrew were awarded the Nobel Prize in Chemistry for the first solved high-resolution structure of protein (myoglobin). Since then, several other studies in crystallography determination of protein structure have been awarded the Nobel Prize[8] until the recent Nobel Prize in Chemistry 2012, which was awarded jointly to Brian Kobilka and Robert Lefkowitz for the structural and functional studies on G-protein-coupled receptors (GPCRs).

With the chemical composition and 3D relative position of each atom in a target, the quest to find hit molecules that could potentially act as drugs has evolved considerably: from a blind screening process that hopes for finding molecular hits essentially by serendipity to an approach often called 'rational' drug discovery and design[5]. In the 80's, this was the case of the first angiotensin-converting enzyme (ACE) inhibitor Capoten

(captopril), the first drug optimized using structural information. In 1997, nelfinavir mesylate (Viracept)—an HIV protease inhibitor—was the first drug with a design completely driven by the structure of the target approved for the US market.[9] These discoveries were only the beginning of a frantic career in search of novel, faster, and cheaper methodologies, and computational algorithms and techniques to develop and design new drugs. Moreover, to sample more compounds over the target (screening process) in less time and to acquire *a priori* key knowledge and expertise to design the library of chemical compounds for further screening in a more precise manner.

II. Material And Method:

2.1. Docking studies: The evaluation of **T-1-MBHEPA** against VEGFR-2 was conducted using the MOE 2019 software (Elkady et al., 2023). A detailed and comprehensive explanation of the findings can be found in the **supplementary section**.

2.2. MD simulations studies: The stability of the VEGFR-2_**T-1-MBHEPA** complex, the strength of interactions, and the differences between the apo and holo structures were evaluated by running a 100-ns classical unbiased MD simulation in GROMACS 2021. The CHARMM-GUI web server's solution builder module was used to prepare the input files (Elkaeed et al., 2022, Elkaeed et al., 2022). An elaborate clarification is included in the **supplementary section**.

2.3. Binding free energy calculation using MM-GBSA: With the use of the gmx_MMPBSA program, we were able to evaluate the binding strength using the Molecular Mechanics Generalized Born Surface Area (MM-GBSA) approach (Elkaeed et al., 2022). An elaborate clarification is included in the **supplementary section**.

2.4. ED AnalysisPCA of the mass-weighted covariance matrix (C) of a selected group of atoms reveals correlated mobility along MD trajectories. In this case, PCA was used to observe the movement of alpha carbons in amino acids (Glu826:Leu1161) (Amadei et al., 1993).

2.5.General Overview of Anticancer Drug Discovery: Due to their intricate, pricey, time-consuming, and difficult tasks, researchers and drug manufacturers have faced significant challenges in the design and discovery of anticancer drugs. 11 Aside from the complexity, first-hand treatments are extremely toxic and do not target cancer cells specifically. 12,13 This is true even though manufacturers are workingon develop novel, selective small-molecule drugs, especially with the aid of in silico developing anticancer drugs. It is therefore of great interest to design and tools that have been developed in recent years. 14 But recently, artificial intelligence (AI) has emerged as a strong and promising technology for quicker, less expensive, and more efficient anti-cancer drug designs than the previously employed CADD. 11 The search for novel drug molecules and the synthesis of more appealing drug molecules can both be sped up by artificial intelligence. Target identification is the first step in the anti-cancer drug discovery process, and after that comes structure-based, ligand-based, and fragment-based screening of successful compounds, de novo anti-cancer drug design for large compounds, anti-cancer drug repurposing, and precise anti-cancer drug reaction prediction. 15,16 Anticancer medications advance as they are discovered from natural products or synthetically, taking into account the toxicity and efficacy of medications and using this artificial intelligence-based advanced technology or previous CADD as a tool for drug design and discovery. As of late, drug repurposing based on promising targets has also become popular. 17–19 However, there are drawbacks to cancer immunotherapy, such as resistance, the ability of cancer cells to evade the immune response, and issues with delivery methods. 20 Nanoparticles using nanocarriers as vehicles have some issues that could solve these issues, according to recent advancements. 21 Because of their special qualities, such as biocompatibility, decreased toxicity, increased permeability, improved stability, precision targeting, and retention effect, 22 nanoparticles can be used to treat cancer.

Structure-Based Drug Design

Which has helped to understand disease at a molecular level [19]. Some of the common methods employed in SBDD include structure-based virtual screening (SBVS), molecular docking, and molecular dynamics (MD) simulations. These methods find numerous applications such as assessment of binding energetics, protein-ligand interactions, and The availability of the three-dimensional structure of the therapeutic target proteins and exploration of the binding site cavity forms the basis of structure-based drug design (SBDD) [18]. This approach is specific and effectively fast in the identification of lead molecules and their optimization conformational changes in the receptor upon binding with a ligand [20]. Being used by many pharmaceutical industries and medicinal chemists, SBDD as a computational technique has greatly helped in the discovery of several drugs available in the market. For example, the discovery of amprenavir as a potential inhibitor of the human immunodeficiency virus (HIV) protease using protein modeling and MD simulations [21, 22], thymidylate synthase inhibitor, raltitrexed against HIV using SBDD approach [23], identification of topoisomerase II and IV inhibitor, norfloxacin which is an antibiotic commonly used against urinary tract infection using SBVS [18], the discovery of dorzolamide, a carbonic anhydrase inhibitor used against glaucoma,

cystoid macular oedema using fragment-based screening [24], antituberculosis drug, isoniazid which is an enoyl-acyl-ACP reductase (InhA) inhibitor discovered through structure-based virtual screening and pharmacophore modeling [25], and flurbiprofen, a nonsteroidal anti-inflammatory drug (NSAID) used against rheumatoid arthritis, osteoarthritis etc. which targets cyclooxygenase-2 (COX-2) discovered through molecular docking approach etc. [26, 27]. The basic steps involved in SBDD consist of the preparation of target structure, identification of the ligand binding site, compound library preparation, molecular docking and scoring functions, molecular dynamic simulation, and binding free energy calculation

III. Conclusion:

Computer-aided drug design has become an important tool in the discovery and development of new cancer therapies. It combines computer algorithms and simulations with experimental data to predict the activity of small molecules against biological targets involved in cancer. This enables the rapid identification of potential drug candidates and the optimization of their properties to maximize efficacy and minimize toxicity With the regularly expanding accumulation of biomolecular structures, constant upgrade of computational power, and enhanced correctnesses in displaying the sub-atomic communications at the nuclear level, it is expected that calculation will play a significantly more vital part in the drug discovery process sooner rather than later. Better understandings of the etiology of illnesses with the assistance of biological system and frameworks pharmacology additionally prompt distinguishing proof of new medication targets and furthermore imaginative combination of drug targets for designing new drugs all the more viably. Hence, the discovery and development of new drugs is considered very expensive and time-consuming. In this respect, computational methods could be constructive for performing different tasks including protein-interaction network analysis, drug-target prediction, binding site prediction, virtual screening, and many others. All these innovative methods could considerably facilitate the anti-cancer drug discovery. In recent years, with the advance of AI, more sophisticated methods, such as retro-synthetic routine plan, drug scaffold generation, drug binding affinity predictions, were developed. The useful predictions generated by computational models combined with experimental validations could further speed up the anti-cancer drug development.

Reference :

[1]. Arriaga E. University of California Press; Berkeley, California: 1968. New life tables for Latin American populations in the nineteenth and twentieth centuries. [Google Scholar]

[2]. Overington J.P., Al-Lazikani B., Hopkins A.L. How many drug targets are there. Nat Rev Drug Discov. 2006;5:993–996. [PubMed] [Google Scholar]

[3]. Imming P., Sinning C., Meyer A. Drugs, their targets and the nature and number of drug targets. Nat Rev Drug Discov. 2006;5:821–834. [PubMed] [Google Scholar]

[4]. Reymond J.L., Blum L.C., van Deursen R. Exploring the chemical space of known and unknown organic small molecules at www.gdb.unibe.ch. Chimia (Aarau). 2011;65:863–867. [PubMed] [Google Scholar]

[5]. Hol W.G. Protein crystallography and computer graphics•toward rational drug design. Angew Chem Int Ed Engl. 1986;25:767–778. [Google Scholar]

[6]. Myers S., Baker A. Drug discovery•an operating model for a new era. Nat Biotechnol. 2001;19:727–730. [PubMed] [Google Scholar]

[7]. Rosenheim O., King H. The ring-system of sterols and bile acids. Part II. J of the Society of Chemical Industry (currently known as J Chem Technol Biotechnol). 1932;51:954–957. [Google Scholar]

[8]. Kaldor S.W., Kalish V.J., Davies J.F., 2nd, Shetty B.V., Fritz J.E., Appelt K. Viracept (nelfinavir mesylate, AG1343): a potent, orally bioavailable inhibitor of HIV-1 protease. J Med Chem. 1997;40:3979–3985. [PubMed] [Google Scholar]