Review on molecular modelling studies of anti-cancer drugs

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Abstract:-
Caner remains a serious threat to global public health, responsible for an estimated 1.5 million mortalities in 2021. While there are available therapeutics for this infection, slow-acting drugs, poor patient compliance, drug toxicity, and drug resistance require the discovery of novel anticancer drugs. Discovering new and more potent drugs that target novel cancer cell line, enzymes is an attractive strategy towards controlling the global cancer epidemic. There has been a need to develop drugs that are less toxic and do not provide resistance in the long run. Thus, this need-based development of anticancer drugs through the use of different molecule has gained its pace since last two decades and there has been a gush among the researchers to apply various approaches in designing anticancer molecules. More specifically, research is being targeted on the utilization of molecular modeling techniques for developing new anticancer agents specifically targeting various cancer cell lines, specific enzymes and tissues. Some of the important and conclusive findings using this approach have been presented in this report.

Keywords: - Anticancer, Molecular Docking, Molecular Modeling, QSAR Studies, 2D QSAR, 3D QSAR, Pharmacophore Modeling.

Introduction

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and multiply (through a process called cell division) to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place.

Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply when they shouldn't. These cells may form tumors, which are lumps of tissue. Tumors can be cancerous or not cancerous (benign). Cancerous tumors spread into, or invade, nearby tissues and can travel to distant places in the body to form new tumors (a process called metastasis). Cancerous tumors may also be called malignant tumors. Many cancers form solid tumors, but cancers of the blood, such as leukemias, generally do not.[1].

Molecular Modelling

Molecular modeling is an efficient way of studying protein–protein interactions. It provides detailed information about how protein residues interact with each other at the atomic level. However, the accuracy of computer modeling is limited by the approximation and assumptions made in the process.[2].

It is currently frequently utilised in physics, chemistry, and biology to explore the molecular structure of huge systems. To simulate the behaviour of molecules in chemical or biological systems, molecular modelling is utilised (Leach, 1996). As a result, it is a top technology with a variety of uses, including spectroscopy, biomaterials, developing materials, and drug creation.[3]. A class of computerised work known as "molecular modelling" could be defined as the application of the laws of physics to the analysis of molecules, including the number and types of atoms, the nature of the bonds, bond lengths, angles anddihedral angles, molecular energy, geometry optimization, enthalpy, and the vibrational frequency of molecular systems. Additionally, nucleophilicity, electrophilicity, electrostatic potentials, and prediction can all be explained by molecular modelling.[4].

These models make it possible to compute the energy for a certain arrangement of atoms and molecules in a particular system, and they subsequently show how the energy of the system varies or changes as the atoms and molecules' positions change. The type of computation, such as energy minimization, molecular dynamics (MD), Monte Carlo simulation, or conformational search, is the second phase in molecular modelling calculations. Calculation analysis is a crucial stage not only for acquiring specific features but also for determining whether the calculations were carried out correctly.[5].

Molecular modelling methods and their usefulness

A key aspect of biology is molecular recognition, which occurs between, among other things, antigens and antibodies, receptors and their signal-inducing ligands, and enzymes and their substrates. Given two molecules in their atomically precise 3D conformations, it's critical to determine whether the molecules attach to one another, if they do, what the formed complex looks like (called "docking"), and how strong the binding affinity is (which can be connected to "scoring" functions).

Molecules lack rigidity. At normal temperature, there is enough motional energy for every atom in a molecule to move continuously. This implies that the relative positions of substituents on a single bond might change over time and that the absolute positions of atoms within a molecule and of a molecule as a whole are not necessarily constant.

One of the main goals in medicinal chemistry is the quest for the so-called bioactive conformation for chemical sets. The biological activity of a drug molecule is thought to depend on a single distinct conformation among all the low energy conformations. Since molecular modelling studies are concerned with the description of the atomic and molecular interactions that influence the microscopic and macroscopic behaviours of physical systems, searching for all low energy conformations is possible.

Using free energy perturbation techniques and a complete atomic-level model with explicit solvent molecules, binding free energy differences between proteins and ligands or, more generally, molecules can be calculated a priori from basic principles. These, however, require a lot of computational power.[6].

Pharmacophore Modelling

The process of discovering and developing new drugs is time-consuming, costly, and complex. Drug discovery and design is a difficult undertaking that requires the use of diverse methodologies. The early to middle stages of the drug discovery process are when computer-aided drug design (CADD) approaches are most often used. With the quick advancement in processing power, data storage, software, and algorithms, CADD approaches have made significant contributions to the drug development process. Target fishing, target validation, hit recognition, lead selection, and lead optimization are all uses of CADD. In this article, pharmacophore modelling, one of the CADD techniques, is reviewed.

Pharmacophore Modelling Principle:-

Paul Ehrlich first proposed the idea of a pharmacophore in the early 1900s. Then, the word "pharmacophore" was created and described as a molecular characteristic that carries (phoros) the required attributes for a drug's (pharmacon) biological action.[9]. In those years, a pharmacophore was thought to be a molecule's chemical or functional groups that are in charge of its biological activity. The International Union of Pure and Applied Chemistry (IUPAC) defines pharmacophore as the combination of steric and electronic qualities necessary for a molecule to interact with a target and subsequently produce biological activity.[7].

Pharmacophore Modelling Application In Drug Development:-

Virtual screening, drug target fishing, ligand profiling, docking, and ADMET prediction all make use of pharmacophore modelling. Future pharmacophore modelling applications are also anticipated to open up new opportunities due to the concept's simplicity and adaptability. In this approach, it may have implications in polypharmacology, drug repurposing, and side effect prediction in addition to the ones discussed above. The articles over the previous 20 years are shown here to demonstrate the breadth of the application of pharmacophore modelling in drug development.

1.Virtual Screening

In virtual screens, pharmacophore modelling is widely used to find drugs that activate the desired biological activity. As a result, scientists create a pharmacophore model that accurately encodes the 3D structure of the intended interaction pattern. In a recent study, medicines available in Drug Bank were repurposed using pharmacophore modelling to combat COVID-19. This study tested a few possible candidates who could be helpful in the battle against the coronavirus pandemic. usages for virtual screening. In virtual screens, pharmacophore modelling is widely used to find drugs that activate the desired biological activity.

2.Docking

There are several ways to integrate docking- and pharmacophore-based molecular modelling techniques. This could eliminate some of the shortcomings of both strategies and produce better outcomes. Pharmacophore models can be used as initial filters to limit the amount of molecules that need to be docked, as pharmacophore guides throughout the docking process, and as filters after docking to choose ligands and rank the poses.

3.Profiling of ligand

In ligand profiling, pharmacophore modelling is used to determine potential targets, as well as their negative impacts and potential novel therapeutic targets. In ligand profiling, both structure-based pharmacophore modelling and ligand-based pharmacophore modelling are used, although structure-based pharmacophore modelling is preferred. For ligand profiling, pharmacophore modelling can be used instead of molecular docking.

4.ADMET

One of the main causes of drug development efforts failing is low ADMET property. Therefore, it is commonly acknowledged that identifying ADMET characteristics at the beginning of the drug development process is essential. Early estimation of ADMET

characteristics using pharmacophore modelling techniques helps to minimise failures while trying to design innovative medicines.[8].

Quantitative structure–activity relationship

Quantitative structure–activity relationship models (QSAR models) are regression or classification models used in the chemical and biological sciences and engineering. Like other regression models, QSAR regression models relate a set of "predictor" variables (X) to the potency of the response variable (Y), while classification QSAR models relate the predictor variables to a categorical value of the response variable.

In QSAR modeling, the predictors consist of physico-chemical properties or theoretical molecular descriptors of chemicals; the QSAR response-variable could be a biological activity of the chemicals. QSAR models first summarize a supposed relationship between chemical structures and biological activity in a data-set of chemicals.

Second, QSAR models predict the activities of new chemicals. Related terms include quantitative structure–property relationships (QSPR) when a chemical property is modeled as the response variable. "Different properties or behaviors of chemical molecules have been investigated in the field of QSPR. Some examples are quantitative structure–reactivity relationships (QSRRs), quantitative structure–chromatography relationships (QSCRs) and, quantitative structure–toxicity relationships (QSTRs), quantitative structure–electrochemistry relationships (QSERs), and quantitative structure–biodegradability relationships (QSBRs). A QSAR has the form of a mathematical model:

Activity = f (physiochemical properties and/or structural properties) + error
The error includes model error (bias) and observational variability, that is, the variability in observations even on a correct model.[9].

Molecules :-

(1)4-oxo-1,4-dihydroquinoline-3-carboxamide derivative.

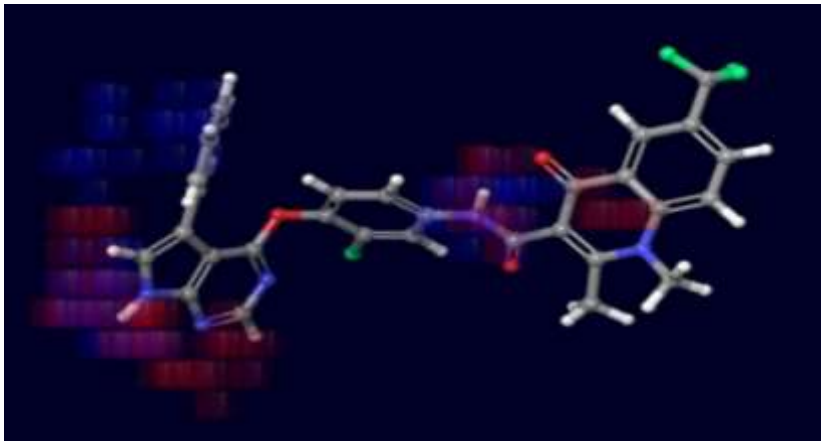

Fig.no.1.1 - 4-oxo-1,4-dihydroquinoline-3-carboxamide

The crystal structure of Axl kinase domain in complex with a macrocyclic inhibitor complex (pdb id-5U6B) had a resolution of 2.84 Å.[10].

(2)Fibroblast growth factor receptors (FGFR) derivative.

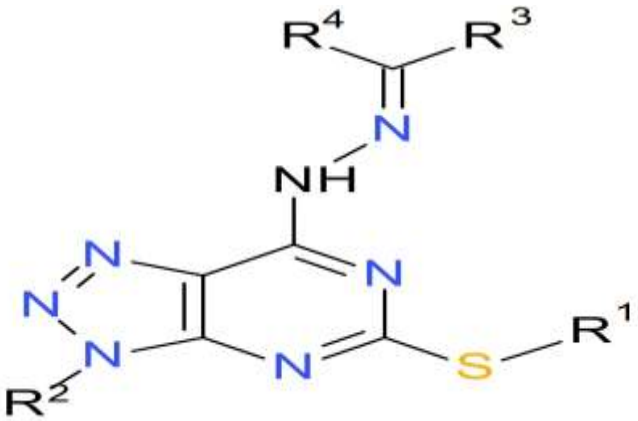

Fig.no1.2. Fibroblast growth factor receptors

In the current study, virtual screening was conducted against the PubChem database using a pharmacophore model generated from the crystal structure of FGFR4 inhibited by LY2874455.[11].

(3)1,2,3-triazolo[4,5-d]pyrimidine hybrid(1,2,3-TPH)

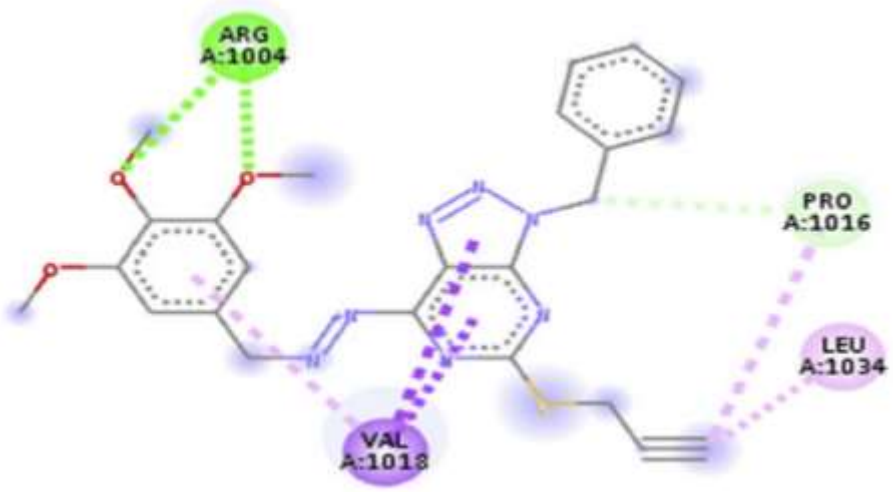

Fig.no.1.3 - 1,2,3-triazolo[4,5-d]pyrimidine hybrid(1,2,3-TPH)

The docking studies showed that2-(1-(2-(3-benzyl-5-(benzylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)hydrazono)ethyl)phenol (A22) having the lowest binding affinity (-8.40 kcal/mol).[12].

(4)Withanolide derivative

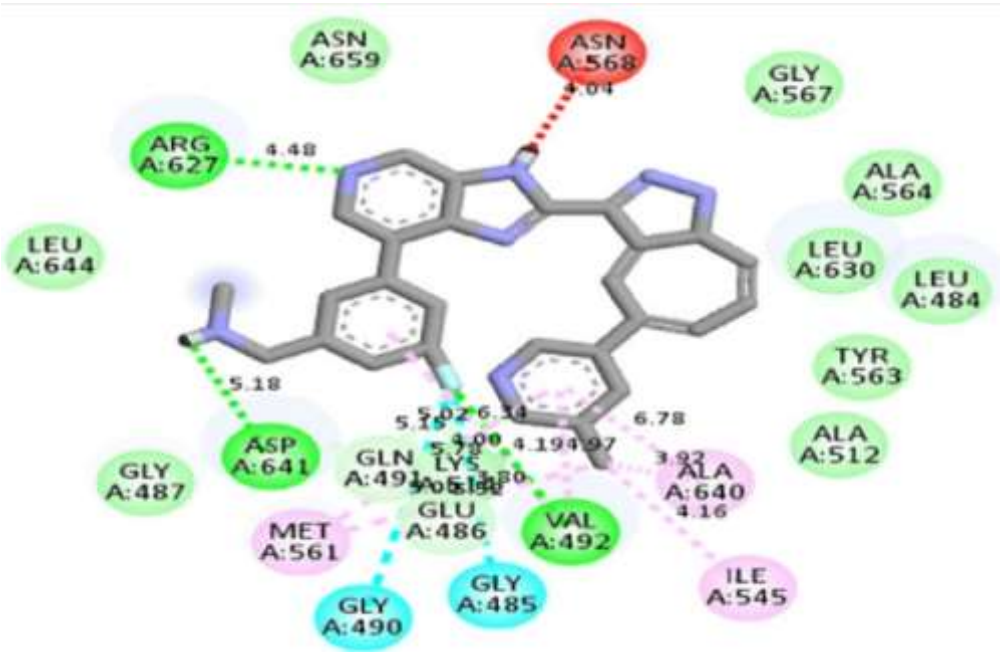

Fig.no.1.4- Withanolide Derivative

The most effective QSAR model for anticancer activity against the SK-Br-3 cell showed the best correlation with activity (r2=0.93 and rCV2 =0.90).[13].

(5)quinazoline derivative

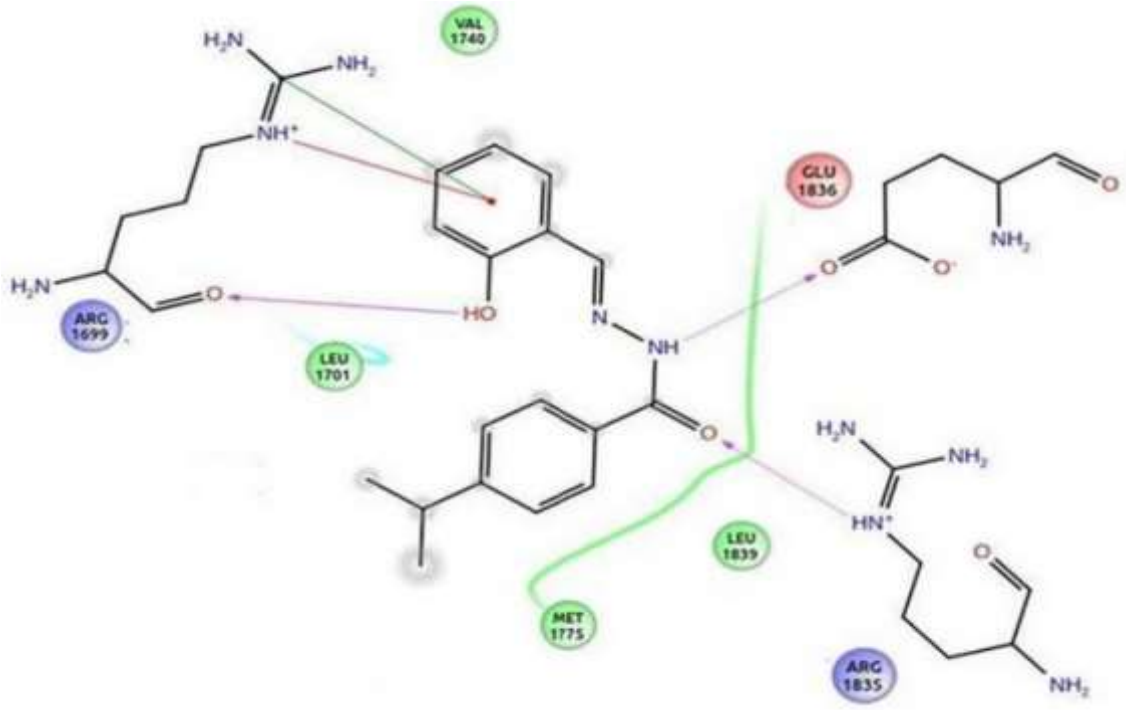

Fig.no.1.5 - Quinazoline Derivative

The aim of this study was conceived to suggest a 2D-QSAR study of a new series of 26 quinazoline derivatives, acting as antitumor agents by the DFT-B3LYP method with the 6 31G base set.[14].

(6)Tubulin Inhibitor

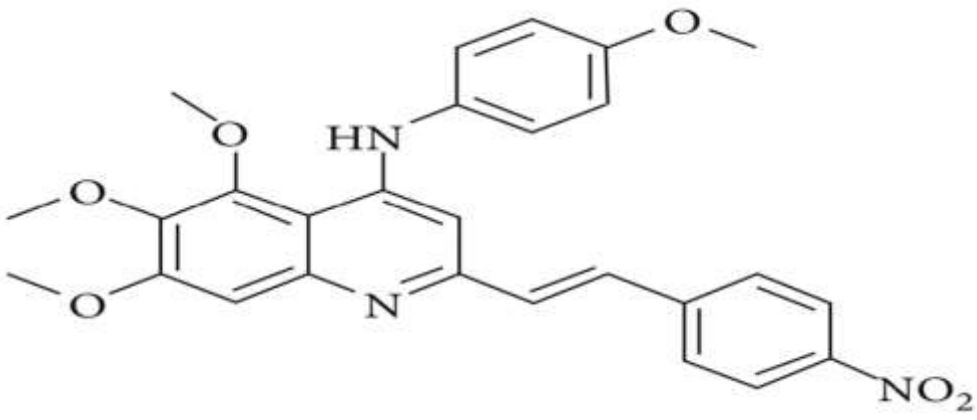

Fig .no.1.6-Tubulin Inhibitor

The model showed a high correlation coefficient (R2 = 0:865), crossvalidation coefficient (Q2 = 0:718), F value and a Pvalue of 5.278e-019 at 6 component PLS level.1061 was used as a 3D query to screen theIBScreen database, and we obtained 1000 compounds. Compounds with a pIC50 value of more than 4 (34 compounds)were selected as the most active compounds. After applyingADMET properties, 10 compounds were selected for furtherdocking studies. Ultimately, compound STOCK2S-23597with the highest docking score (-10.948 kcal/mol) wasselected as a potent tubulin inhibitor.[15].

(7)Synthesis, anticancer, molecular docking and QSAR studies of benzoylhydrazone

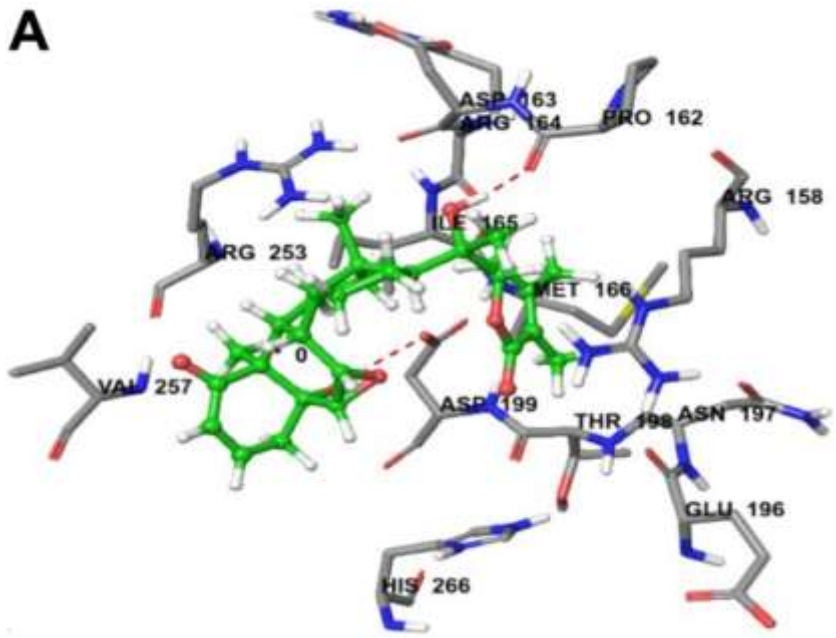

Fig.no.1.7 - Benzoylhydrazone Derivative

Synthesis of 4-isopropylbenzoylhydrazones was carried out by reacting and refluxing4-isopropylbenzoylhydrazide with varied aldehydes 1–30 inmethanol for 3–4 hrs. In methanol the crude product was recrystallized and obtained 78–92% yield.[16].

(8)Xanthone Derivatives

Fig.No.1.8- Xanthone Derivatives

The present study deals with the multiple linear regression-QSAR modeling for xanthone derivatives against human cancer cell line HeLa and anticancer target Top2A. Four compounds (X-19, X-44, X-45, and X-49) were screened out through the QSAR model, docking, ADMET screening, and synthetic accessibility[17].

Need Of Work

1.Structure-Based Pharmacophore Mapping

The pharmacophore mapping approach has advanced over the past few decades and is now regarded as one of the most important technologies for the drug discovery process. To enhance pharmacophore modelling, which has been extensively utilised for virtual screening, de novo design, and lead optimization, many types of structure-based techniques have been undertaken. Another important technique is the structure-based pharmacophore (SBP).

2.LIGAND-BASED DRUG DISCOVERY

Comparability Search A notion known as molecular similarity serves as the foundation and driving force behind ligand-based techniques in drug development. According to this idea, compounds tend to have comparable biological effects because of their significant structural similarity. To put it another way, ligand-based drug discovery techniques rely on the structural details of the active ligand that interacts with the target protein, and a compound like this with interesting biological properties can be used as a query template to find and predict new chemical entities with comparable properties.[18].

3.QSAR Modeling

Another ligand-based method that analyses the biological activities of medications using different molecular descriptors (MDs) or fingerprints is called QSAR (Quantitative Structure Activity Relationship) (FPs). According to the structural properties of the ligand, these models mathematically explain how the activities react to the targets. The development of QSAR models has also utilised a variety of machine learning (ML) and deep learning (DL) techniques, such as Support Vector Machines (SVM), Random Forests (RF), Polynomial Regressions (PR), Multi Linear Regressions (MLR), and Artificial Neural Networks (ANN).

4.USING MD SIMULATION TO FIND NEW DRUG BINDING SITES

Many important biological events rely on the information of protein-ligand complex interactions. The recognition and characterization of LBP is the key to understand the function of endogenous ligands and synthetic drug molecules. GPCRs perform an important role in a variety of physiological processes. GPCRs are a class of commonly used targets in drug discovery Recent discovery indicated that beside binding to orthosteric sites, ligands could bind to different allosteric sites that are far away from the targeted binding pockets.[19].

Future Scope

The market for drug discovery informatics is anticipated to increase from 1.5 billion in 2016 to 2.84 billion by 2022, and it might keep growing after that. As a result, there is a growing need for the development and application of new informatics solutions. The shift from purely academic research to clinical care is one of the main forces propelling the growth of the global market. The high cost of informatics software, interdisciplinary backgrounds, and more highly skilled workers may have a significant impact on the expanding market. Currently, a lot of well-known programmes are offered as either free software or services or as commercial software. To fully exploit the potential of this effective approach, several obstacles still need to be overcome. However, in the context of pharmacology, the synergistic element is a crucial chemical phenomena wherein two distinct biomolecules from different origins can combine to produce an exponential effect that is bigger than the sum of their individual effects. Because a molecular docking approach has not been developed to assess a certain structure in a specific scoring function, it can be secondary if it is found that a particular structure is more favourable in terms of the docking score and it may be connected with synergism. By distinguishing between synergistic, additive, or antagonistic effects, which may be described both qualitatively and quantitatively, a linear/quadratic formula could be created to assess synergy. In this regard, additional research is required to determine how the chemosensitivity between a macromolecule and ligand could be identified when several ligands are present. Even if it is challenging due to the overwhelming amount of data, it is possible to evaluate the tiny targets that are most constrained to the studied binding site, particularly in drug-protein analysis. A more thorough approach needs to be taken when developing system biology models that rely on a medication synergy test, maybe by combining qualitative and quantitative aspects. In this way, an unique input for computational docking analysis might be created, allowing for things like the measurement of molecular signalling that has been proven to be present in a number of different parts, ligands, or targets. To increase the accuracy of experimental data, drug synergy research may be supported by these systematic synergy modelling techniques. For continued progress, the molecular structure databases must be improved. To improve the quality of the structural models they contain and increase the trustworthiness of the outcomes, filters are required. With more than 150,000 empirically validated 3D models, the PDB, which was founded in 1971 as a pioneering crystal structure database, is now the most popular source for molecular in silico modelling[20].

Conclusion

In conclusion, molecular modelling studies of anti-cancer drugs have proven to be a valuable tool in the discovery and development of new and effective treatments for cancer. These studies have provided important insights into the molecular mechanisms of drug action, and have helped to identify new drug targets and potential drug candidates. The use of molecular modelling techniques has also been useful in predicting the potential side effects of new drugs, and in designing drugs that are more specific and less toxic. However, it is important to note that molecular modelling studies are only one aspect of the drug discovery process, and that further experimentation and validation is required to confirm the results obtained through these studies. Overall, molecular modelling studies have made significant contributions to the fight against cancer, and will continue to be an important tool in the future development of new and effective anti-cancer drugs.

List Of Figure

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