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Review Article

A Brief Review on Smart Drug Design in Favour of Improving Health Indicator

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A B S T R A C T

The drug is a vital need in contemporary scenarios. Relevant to the traditional methods of drug designing like structural-based drug design and computer-aided drug design, Molecular Docking (MD) is a more complicated and intelligent tool. Approaching the precise three-dimensional binding site or pose of the drug candidate with the receptor is the target of ligand-receptor docking. It calculates the preciseness of drug candidates with receptors. Lead optimisation is assessed by the combinatorial libraries and provides the beneficial or harmful consequences of drug-receptor interaction. It can be difficult to interpret the outcomes of stochastic search methods and establishing the input structures for docking is just as important as docking itself. Based on the system's overall energy, docking simulations forecast an optimum docked conformer. Despite all viable strategies, the difficulties still lay in ligand chemistry like tautomerism and ionisation, the rigidity of receptors like multi-confirmation of the drug candidate for the same receptor, and the interaction of the drug with the precise binding site. This article briefly discusses a few significant features of MD, including its techniques, kinds, applications, and problems.

Keywords: MD, Ligand, Molecular Modeling, Drug Discovery

Introduction

Designing and producing substances utilised in the health era for improving health indicators is referred to as medicinal chemistry. The study of currently available medications' biological characteristics and structure-activity correlations (SARs) is a component of medicinal chemistry. It takes a long, arduous, and expensive process to find new drugs with the appropriate therapeutic activity. There is a vast number of drug candidates approved for the respective health issue but only up to a hundred may be evaluated for safety, and approximately ten molecules may be undergone for a human clinical trial. Drug designing and introduction in the market is a time-exhausting and cost-effective process. Despite the large upfront expenses, improvements have been made in the prevention and management of human illness. Although drugs entering the market is important; it is not the criterion of success. Humans first began utilising chemicals to treat illnesses many centuries ago. Hippocrates advocated the use of metallic salts medicines, such as cadmium oxide, iron sulfate, and copper and zinc salts. Carpensis used mercuric chemicals to cure syphilis in about 1500 A.D. Wohler created urea in 1852, the first organic substance to be created in a lab. Salicylic acid, Phenazone, Acetylsalicylic acid, Barbituric acid, Morphine, Cocaine, Sulfamidochrysoidine, Chlorpromazine (CPZ),

Grignard reagents, and others were created between the eighteenth and nineteenth centuries; although its mechanism, pharmacokinetics, pharmacodynamics factors were studied later.[1]

Basically, most of the drug targets are protein in nature. A ligand is positioned into the precise binding site of the target-specific receptor randomly either stable or temporarily complex with possible efficacy and efficiency. Energy phenomenon is the fundamental concept that can be suggested using the information gleaned through Molecular Docking (MD). Currently, MD is targeted to anticipate the potential binding interaction of the ligand-receptor earlier. It shows us how small molecules of receptors are considered as the binding site and shed light on pharmacodynamic and pharmacokinetic features by MD.[2]

As civilisation explored the techniques for improving health indicators, several new diseases have been grooming in the world like COVID-19. Even there are drugs designed based on personalised genome structures for an individual patient through 3D printers. In this approach smart medicine, artificial intelligence, digital twin, blockchain integration, and 3D printing for the development of customised organs for patients have been added to the till date. Virtual screening is a more straightforward and logical approach to drug discovery than conventional experimental high-throughput screening (HTS), and it has the advantage of being both inexpensive and effective. The two types of VS are ligand-based and structure-based. The use of ligand-based approaches, such as pharmacophore modeling and quantitative structure-activity relationship (QSAR) methodologies, is possible when a set of active ligand molecules is known and little to no structural information about targets is available. It was initially in 1980 that the MD concept became prevalent. Since programs grounded on various algorithms have been created to undertake MD investigations, docking has become a more crucial technique in pharmaceutical research.[3]

Cambridge Structural Database (CSD), Available Chemical Directory (ACD), MDL Drug Data Report (MDDR), and National Cancer Institute Database (NCI) are the various database to get the information relevant to the small ligand. Different interacting conformers are produced and equated to one another while docking is being done. When a conformation is rejected, new conformers are found, and the searching for an appropriate drug candidate is repeatedly done until it reaches its goal. Different scoring systems, such as consensus scoring, are used to get around this issue and avoid false positives.[4]

MD: Smart Drug Designing

Interaction of ligand and a receptor site are coupled to one another to create a constant complex, a method known as docking in the field of molecular modeling can predict the possible orientation of a drug candidate to the receptor site. Because it can anticipate how tiny molecule ligands will attach to the proper target binding site, MD is a popular technique in structure-based drug design. The characterisation of binding behavior is crucial for the rational design of drug candidates and for illuminating basic biochemical mechanisms. Molecules are arranged in maximum beneficial configurations for interaction with a receptor during docking. Docking is the process in which a drug candidate produces stable interaction within the binding site for therapeutic effect.[5]

The mechanical programming of Westheimer et al. and Huckel and Mullikan's concepts of molecular orbitals serve as the foundation for MD procedures. Protein structure and medication data are both provided separately, however, there is a lack of additional information. Docking is the technique of rationally creating two or more molecules and fitting them into the 3D space in complementary ways (Figure 1).[6,7]

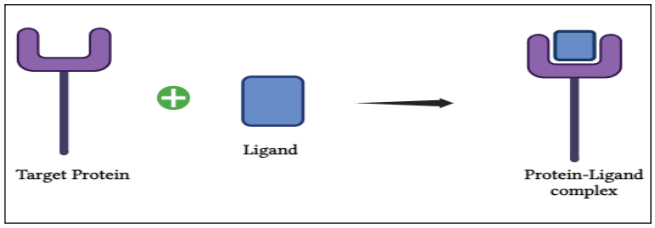

Figure 1.Hypothetical Representation of MD

Contemporary Approach of Molecular Modelling

The term "molecular modelling" refers to a series of methods that use computer-generated images of chemical structures to depict the respective positions of all the atoms in the molecule under study, as well as to mimic the dynamics of such molecules and their spatial ordering. Such methods can shed light on a variety of molecules' physicochemical characteristics as well as on their potential role, or more specifically, their function, within an organism. As a result, they can be particularly useful instruments for examining structure-function links. Furthermore, an intelligent tool for creating, characterising, and changing the configurations and confirmation of drug candidate and receptor interactions as well as the pharmacokinetic and pharmacodynamic behaviour of these molecules covers in molecular modeling as seen in Figure 2.[8]

The goal of MD is to apply Artificial Intelligence (AI) to predict ligand-receptor interaction. Ligand sampling and applying the scoring function are the two parts of the docking process. Sampling algorithms aim to find the most stable conformation of the ligand which fits within the protein's active binding site, which is then scored using a

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scoring system. The modeling of two molecules interacting is a challenging task. Electrostatic, hydrogen-bonding, van der walls, and stacking interactions are the force that exerts the intermolecular interaction of the drug candidate and receptor site. The scoring functions and a search algorithm can both be used to explain docking protocols Figure 3.[9]

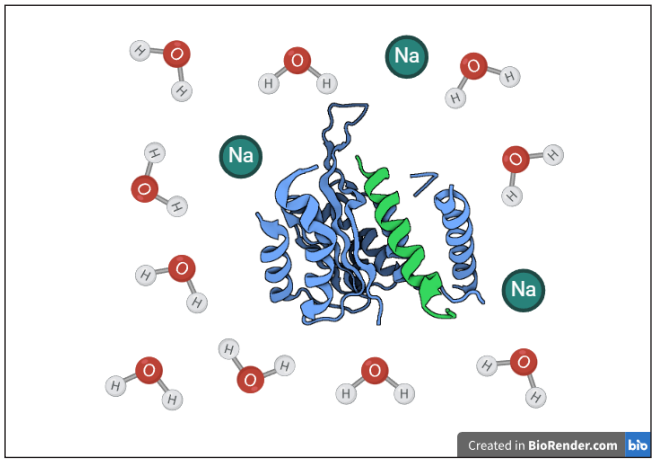

Figure 2.Hypothetical Representation of Molecular Modelling

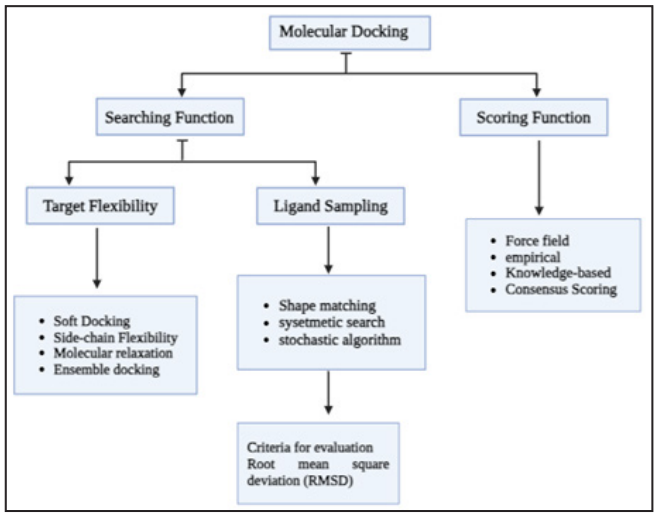

Figure 3.Distinctive Method Employed for MD

The optimal configurations contain the empirically discovered binding pose should be produced by the search method. Despite the fact that a thorough search algorithm would examine every potential mode of interaction possibility within the two molecules, this search would be impracticable because the restriction of of the search site and the long time to accomplish. Because a slight part of the entire conformational space can be sampled, need to estimate the computing cost and the size of the search space explored.[10]

Systematic, stochastic, and deterministic search techniques are the most common categories. The degree of freedom for each ligand is incrementally explored by systematic search techniques. The number of assessments may experience a combinatorial explosion; free bonds can arise. The comprehensive, incremental structure relies on ligand fragmentation, and conformational ensemble; fragment-based techniques are used by FlexX and eHits; incremental construction and graph matching, respectively.[11,12]

Random modifications to the ligand freedom are made by stochastic search techniques. This form of procedure does not, however, ensure convergence to the ideal answer. It can be improved through an iterative process. Monte Carlo, Evolutionary Algorithms along with genetic, Tabu Search, Swarm Optimisation, AutoDock, GOLD, DockThor, and MolDock are stochastic algorithms to evaluate the freedom of ligand bonds.[13-15] But this kind of approach has a high computing cost and frequently traps the resulting conformations in minimum energy, which is undesirable. Examples include molecular dynamics (MD) simulations and energy minimisation techniques.[16,17]

Integrated Function of MD: Scoring Function

Aim of scoring function; an assortment of mathematical techniques is to evaluate the binding affinity through a non-covalent interaction. The creation of an energy-scoring function that can quickly and properly represent the protein and ligand interaction is a significant issue in all computational techniques. Initial step is to identify the drug receptor interation; challenges for lead optimisation. Next application is structure-based drug design; to find potential therapeutic hits respective drug target.[18]

Value of scoring function's determine the pose avalability, drug candiddate activity instead of calculating the protein-ligand binding affinity. It helps to make several assumptions and simplifications. Knowledge, force-field, and empirical-based are three different categories to measure the scoring functions. Basic force-field-based scoring functions calculate the binding energy as the total of the non-bonded (electrostatics and van der Waals) interactions. Columbic framework is used to calculate electrostatic interaction.[19,20] whereas distance-dependent dielectric function is often used to control the involvement of charge-charge interactions; it is challenging because it describes the actual energy environment of protein surrounding. Consensus scoring is the latest technique to evaluate the different scoring functions and combine them. It enhances enrichment and the prediction of receptor site conformations and sits through virtual screening. The predictions made by binding energies could still be incorrect. The usefulness of consensus scoring declines when terms in various scoring functions are strongly related. A ligand is only approved for the drug candidate if it passes all remarks of the scoring function. DOCK, ChemScore, PMF, GOLD, and FlexX are the softwarethat merges the scoring function.[21]

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Huge number of scoring function can be computed through MD. Few of them discussed in the next section.

Extensions of Force-Field-Based Scoring Functions

It consists of hydrogen bonds, solvent effect, and entropy. User-friendly software applications like DOCK, GOL, and AutoDock provide these features. The way hydrogen bonds are handled, the structure of the energy function, and other things differ between them.[22]

Empirical Scoring Functions

Energy break down in form of hydrogen bonds, ionic interactions, the hydrophobic effect is calculated by empirical scoring functions. By using regression analysis ligand-protein complexes set with known binding site generate the regression coefficients. Energy term evaluation for empirical scoring functions is rather straightforward. [23]

Knowledge-Based Scoring Systems

Statistical method of ligand–protein interaction is used to to determine the interatomic interaction frequencies. They are predicated on the idea that interactions will occur more frequently the more pleasant they are. Ligand and protein is computed a score by encouraging favored associates and exhausting repulsive interactions within a predetermined cutoff. PMF, DrugScore, SMoG, and Bleep are the knowledge-based scoring function.[24]

Consensus Scoring Function

It combines a number of discrete scores to assess the docking conformation. When drug candidate undergo through a variety of scoring methodologies, possibility of acceptance enhanced. In virtual screening, it determine the proportion of strong ligands among the high-scoring ligands and enhances predictions of bound conformations and poses. Strong correlation between the numerous scoring function reduce the consensus scoring. DOCK, ChemScore, PMF, GOLD, and FlexX scoring is collectively called CScore.[25]

Docking Methodologies

Docking of Rigid Ligand and Rigid Receptor

Most of the time ligand and receptor exhibits the regidity with each other. In this case, ligand flexibility might be addressed by using a pre-calculated set of ligand conformations. The ligand and receptor were kept rigid during the docking process using an early version of DOCK, FLOG, and some protein-protein docking systems like FTDOCK.[26] A clique detection method is used to superimpose sets of spheres that represent the ligand and receptor. The amended versions now include an incremental creation technique and an comprehensive search to take ligand flexibility into account.[27] FLOG uses a search method to calculate the sets of distances between ligand and receptor; pint out the exact location of the binding site that needs to be connected to ligand atoms. This technique is helpful if a crucial interaction is previously known to docking.[28]

Docking of Flexible Ligand and Rigid Receptor

For the stable interaction between the ligand and receptor, minimum energy should be produced. However, the cost is very expensive if the receptor is also flexible. The most adapted attitude is that ligand should be flexible and receptor site should be rigid during docking; AutoDock and FlexX, have adopted this idea (Figure 4).[29]

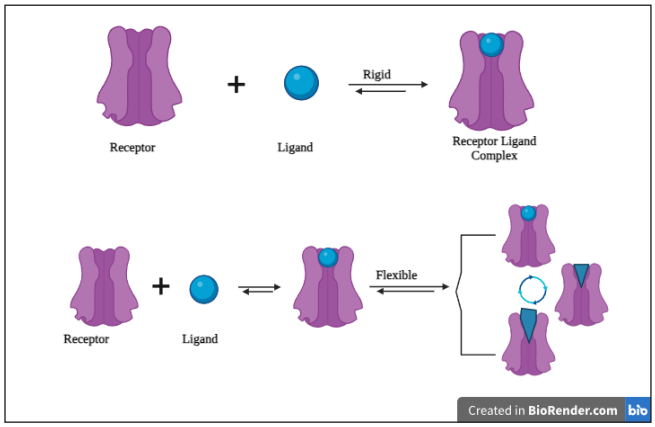

Figure 4.Hypothetically Representation of Interaction between Ligand and Rigid Receptor

AutoDock 3.0 uses evolutionary, genetic, and Lamarckian genetic algorithm techniques to express the flexibility of ligand and rigidity of receptor site. version of AutoDock; AutoDock Vina allows for the evaluation of protein-protein interactions.[30,31]

Flexible Ligand and Flexible Receptor Docking

Receptors are generally protein in nature possessing inherent mobility; therefore, flexible docking is being challenges. Beside the degree of freedom, high computing costs are another barrier. In addition to the traditional induced fit, several theoretical models have been put forth to demonstrate the flexible ligand-protein binding process.[32] These models include conformer selection and conformational induction.[33,34]

Basic Approaches of MD

Simulation and Shape complementarity are approaches used for performing MD.

Simulation Approach

Due to the significant energy release, this method is more reliable for MD. Ligand and receptor site are physically separated before the ligand is permitted to bind into the groove of the target following “certain periods of moves” in its conformational space. There are torsional angle rotations, ligand’s structure and rotations and translations.

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Every time the ligand moves within the conformational limit, "total energy" is released. This strategy is more beneficial due to accepting ligand flexibility, evaluating the molecular recognition between the ligand and the target. Fast optimisation techniques and grid-based tools are the advanced features which make it mor favorites to the researchers.[35]

Shape Complementarity Approach

Surface behavior of ligand and receptor site is monitored by this method. In this example, the molecular surface of the ligand is illustrated in terms of the surface area of the target that is accessible to solvents. It is fast and scanning through hundreds of ligands to find the appropriateness of binding characteristics on the target molecular surface. The interfaces of biological assemblies, such as protein-protein complexes, are characterized by shape complementarity. It does not represent a physical interaction, but it exhibits a strong correlation with some interaction energies, including non-polar desolvation and van der Waals. As a result, it has been extensively employed in protein-protein docking to look for and assess potential protein-protein binding mechanisms.[36,37]

Strategies Involved in the MD

Drug designing has been completely developing the way that research is done. It is an initial point for the development of logical drugs.

Drug-DNA Interaction

Drug interaction with nucleic acid, MD is crucial; cytotoxicity can be assessed by using this information. This concept is very useful in anticancer treatment. The practical approaches are suggested to measure the interaction of binding pose and receptor. Additionally, this information might be useful in identifying medication structural alterations that might lead to sequence- or structure-specific binding to their target.[38]

Identification of Hit Molecule

Scoring function helps to find the hit in huge databases of effective drugs. Through virtual screening, interaction of ligand and receptor can be visualised. Virtual screening, conventional high-throughput screening, and fragment-based screening are the substantial techniques to find the hit.[39]

Lead Optimisation

Through a targeted screening funnel comprising both in vitro and in vivo experiments, both the biological activity and the characteristics of the lead series. This can be utilised to create medication candidates that are more powerful, selective, and effective. Iterative rounds of synthesis and characterisation are used to establish a bond between the proposed chemical structure and therapeutic activity.[40]

Bioremediation

Some drugs act through the enzyme inhibition and stimulation. Bioremediation is the technique by which pollutants can be predicted for the breakdown of certain enzymes. Enzyme identification and method of action can be accomplished using MD. It can also be used to ascertain how proteins are related to one another. Remediation is a virtual screening procedure for molecules.[41]

Docking Software for Drug Designing

Still there are number of issues associated with docking; researchers continuously conduct a thriving investigation focused on them. The conformational search algorithm and the scoring function are two key features of the docking process. Binding consequences could be predicted through binding free energies, however binding free energies difficult to compute if subtraction of huge figures. These huge figures are the interaction energy between the ligand and protein.[42] Some of the software systems are listed below:

Cell-Dock

Based on surface complementarity and electrostatics, it also scans the molecule on basis of the translational and rotational space. To perform effective multiple conformation rigid body docking, shape complementarity between the ligand and protein was added. To execute rigid body docking, ligand and protein interaction is further improved by a Gaussian shape fitting function in FLOG, CLIX, FRED, and PAS-Dock (Protein Alpha Shape-Dock).[43]

AutoDock

Monte Carlo simulated annealing, the LGA energy minimisation is the approach implemented in the AutoDock. AMBER force field model is used to analyses potential. Using a Lamarckian Genetic Algorithm and an empirical free energy force field, AutoDock quickly predicts bound conformations with expected free energies of association.[44]

DOCK

A clique detection method is used to superimpose sets of spheres that represent the ligand and receptor. The geometrical and chemical MAs are used to score the ligand-receptor complexes, and steric fit, chemical complementation, and pharmacophore similarity are all taken into consideration. The improved versions now incorporate an exhaustive search and an incremental construction technique to take ligand flexibility into account. One of the most popular and commonly utilised ligand-protein docking technologies is DOCK. Hard ligands were used in the initial iteration; flexibility was later introduced by gradually adding more ligand to the binding pocket. As previously mentioned, DOCK is a fragment-based strategy that creates diverse ligand orientations by combining complementary shape and chemistry methodologies.

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GOLD (Genetic Optimisation for Ligand Docking)

In recent years, gold has seen a significant increase in users due to its impressive performance in independent tests. The protein is thought to be stiff other from that. It is advantageous when the binding pocket has amino acids that form hydrogen bonds with the ligand. The development of GOLD is currently concentrated on developing the computational algorithm and adding support for parallel processing.[45]

FlexX

FlexX-Scan was created with the intention of accelerating the virtual screening procedure even more. A compact descriptor for characterising advantageous protein interaction sites within the protein binding site has been created based on the incremental building docking tool FlexX. Utilising specialised clustering methods on the typical interaction points produced by FlexX, the descriptor is computed.[46]

A fragment-based strategy called FlexX makes use of tough proteins and pliable ligands. Using the MIMUMBA torsion angle database, it generates conformers. FlexX and DOCK both use fragment-based techniques, but their results are substantially different. Contrary to DOCK, which functions well with polar binding sites, FlexX operates radically differently.[47]

A plethora of docking software has been employed in drug discovery and design. Table 1 is the summary of a few of them along with their therapeutic potential.

Table 1.Summarisation of Docking Software

Docking	Algorithm	Uses
MOE[48]	Graphic based fast speed	It is flexible, easy to operate, able to compute interaction consequences with amino acids with binding sites.
ICM*[49]	Monte Carlo minimisation	It is collection of different scoring function.
GLIDE**[50]	Monte Carlo	It is used to design lead discovery and optimization.
PyRx[51]	Lamarckian genetic algorithm	It is suitable to temperature sensitive algorithms.
PyRx[52]	Lamarckian genetic algorithm	It is suitable to temperature sensitive algorithms.
FRED[$53]	Exhaustive search algorithm	Non-probabilistic approach to screen the maximum possible active site at receptor for the interaction
FITTED[$$54]	Genetic algorithm	Compute the hydrogen bonding potential on protein–ligand complexes
Glam Dock[55]	Monte Carlo method	It is used to determine the 2D analysis to screen ligands by targeted receptor protein.
iGEM DOCK[56]	Genetic algorithm	It correlates the data between the structure-based virtual screening and post-screening analysis; and provide the graphical integrated setting for virtual screening.
GOLD[57]	Genetic algorithm	It is employed to establish atomic imbrication between receptor protein and ligand.
Auto Dock[58]	Lamarckian genetic algorithm	It is user-friendly.

*: Internal Coordinate Modeling
**: Grid-based Ligand Docking with Energetics
[$]: Fast Rigid Exhaustive Docking
[$$]: Flexibility Induced Through Targeted Evolutionary

Description

It is obvious that docking software is the inherent part of artificial Intelligence which entirely depends upon the artificial intellectual. User can operate the software, but number of the complexities associate with it. These compliances are considering as challenge of the docking; however, resolution of these barrier could be developing the more efficient approach to define more precise and prediction of new molecule without harming the living being. A few constraints of the docking software are discussed in the below section.

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Reliability

Lack of confidence about the scoring functions which do not offer the precise binding energies. It could be due to compliance intermolecular interaction variables. Let us assume that guanidine-arginine interactions and halogen bonding are both established to find out the affinity interactions but not useful for that receptor. affect the affinity of the protein-ligand binding but are not taken into consideration.[58]

Difficulty to Target the Hydrophilicity Interaction

It is the open issues in the binding pocket due to tinies atoms distribute light incompetently, and hydrogen coordinate bond could not identify through x-ray crystal structures. Next compliance is that it could not define the accurate interaction with water molecules and how strong that influence will be. Unfortunately, it is unable to define that how hydrogen bonding network affected by ligand binding and how many water molecules in the binding pocket will be substituted by ligands.[59]

Computation of Receptor Rigidity

Receptors are associated with rigidity; therefore, ligand bind to the active site is the main scoring function in the docking tool depending upon its shape and configuration. Individual receptor configuration represents only individual rigid receptor conformation. Docking tool unable to predict that a receptor protein could be in regular movement between plethora of structural states with comparable energy.[60]

Contribution of Docking Studies in Health Management

Hypertension/ High Blood Pressure

It is a biophysical parameter in the living system; a plethora of the disorder associated with it viz. include left ventricular hypertrophy, coronary heart disease, renal chaos, and heart failure. lysine deficient protein kinase 1(WNK1), Serine/ threonine protein kinase (WNK4), FGF-binding protein (FGF-BP, FGFBP1, BP1), Angiotensin-1-converting enzyme (ACE) and angiotensinogen (AGT) gene have been studied as the blood pressure regulating gene earlier.[61-64]

ACE plays a dynamic role in hypertension management. It controls the conversion of Angiotensin-I(decapeptide) into Angiotensin-II (octapeptide) i.e., most powerful vasoconstrictor account in our body. The possible poses at the ACE for Teprotide, Fosinopril and Allicin were predicted through the MD which is expanding as a critical tool in the domain of drug discovery and designing. −20.1163, −18.9225, −5.5448 was the S-score value computed for the Teprotide, Fosinopril and Allicin accordingly.[65-67]

MOE (Molecular Operating Environment) is docking software used for the screening, investigating, and evaluating the protein compatibility with other proteins or ligands. It is based on the graphical illustration of ligand and receptor affinity poses along with their position and interactions.[68,69] S-score is the measurement tool of MOE software that lies on receptor-ligand interaction consequences, salt bridges, hydrogen bonds, lipophilic bonding, cation-, and solvent contact. Low S-score of inhibitors indicated the strong interaction with ACE at active sites.[70]

ACE inhibitors were targeted to the ACE target protein's pocket through Generalized Born solvation model (GBVI) score function. A force field-based scoring function termed as the GBVI/WSA dG computes the free energy of binding of the ligand from a specific alignment.[71]

Teprotide, a natural biomolecule isolated from (Bothrops jararaca) venom has been shown the best interaction of ACE by MOA. However, a synthetic compound Fosinopril followed the best interaction after ACE after teprotide. It is used as an orally effective drug for the treatment of high blood pressure. Although Allicin an active constituent of Allium Sativa (Garlic) exhibited a highest S-score, therefore poor affinity interaction between protein-ligand but due to its herbal nature it can be design as the antihypertensive agents.[72]

Breast Cancer

ER (Estrogen Receptor), PR (Progesterone Receptor), EGFR (Epidermal Growth Factor Receptor), and mTOR (mammalian Target of Rapamycin) impart the invasion of breast cancer. Targeting to these receptors dissemination of the disease could be an effective approach. Furanocoumarin, analogue of coumarin, was identified by employing Structure Based Multitargeted MD Analysis to counteract breast cancer.

More than twenty analogues were predicted of furanocoumarin as anticancer potential viz. Xanthotoxin, Apterin, 6,7-Dihydroxy bergamottin, Marmesin, Methoxsalen, Imperatonin, Isopimpinellin, Trioxsalen, Bergamottin, and Phellopterin though the BioSolveIT FlexX docking program. These analogues confirmed their interaction to the ER, PR, EGFR, and mTOR receptor targets compared with the reference compound i.e., 4-hydroxy tamoxifen (TAM), Ulipristal acetate, AEE788, and Rapamycin (RAP), enlisted in the Protein Data Bank (PDB). These were analysed for the docking energies, the bioactivity score for oral administration, molecular characteristics, interaction consequences and so many more. Five analogues had high strong interaction with receptors.[73-75] Figure 5 is the depiction of compound as anticancer identified by different docking studies.

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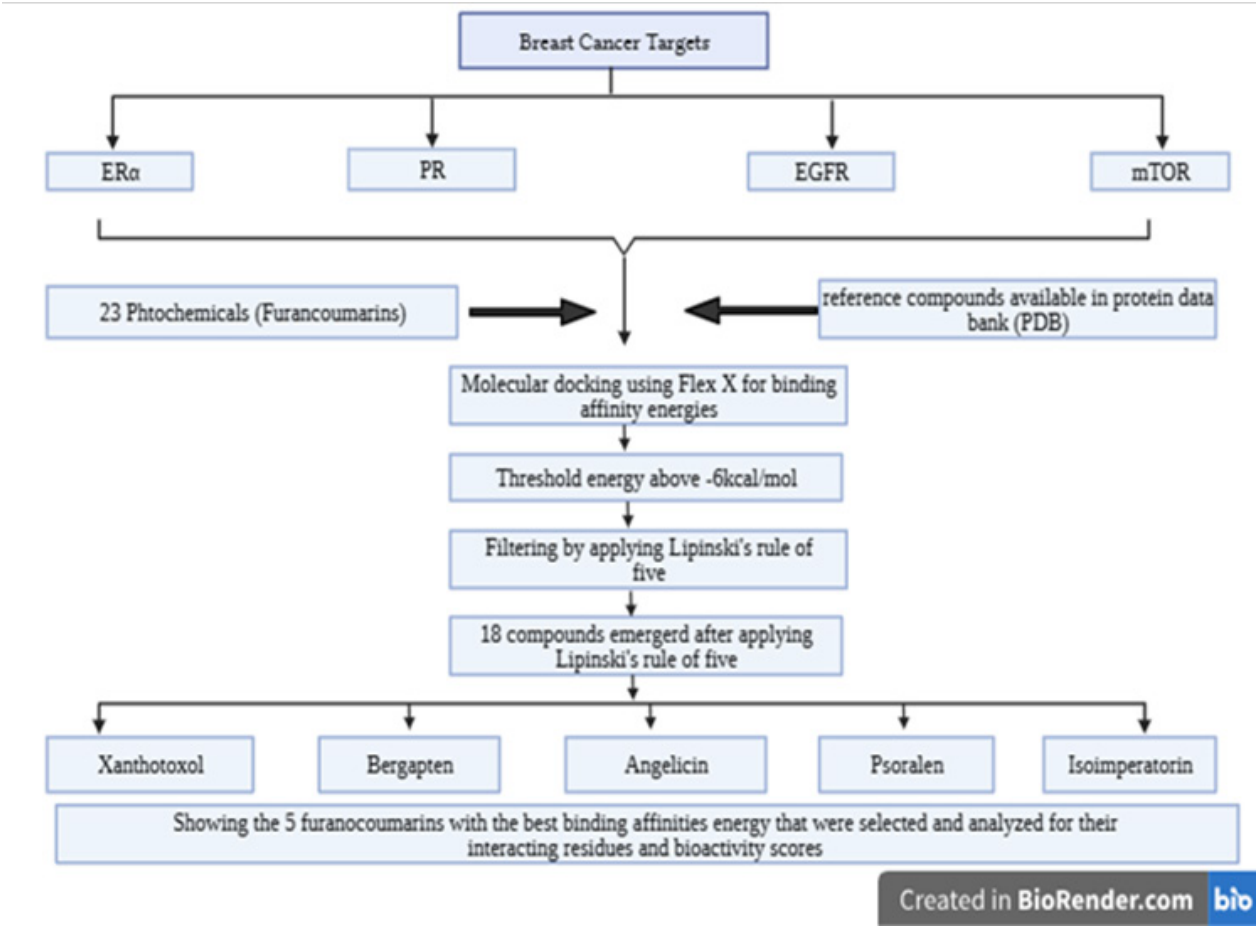

Figure 5.Depiction of Anticancer Compound Developed by Docking

Alzheimer's Disease (AD)

AD can be diminished by targeting the two receptors i.e. β-amyloid protein and acetylcholinesterase enzyme. In silico MD studies of bio constituent obtained from the chloroform leaf extract of Carissa carandas were studies to screen their Anti-AD potential. iGEMDOCK software was employed to target β-amyloid fibril and recombinant human acetylcholinesterase ligands for their anti-AD potential in reference to galantamine and curcumin. The best docking scores were obtained for 1-heneicosanol; N-nonadecanol-1; cholesta-4,6-dien-3-ol, (3β); di-n-octyl phthalate; 7,9-di-tert-butyl-1-oxaspiro (4,5)deca-6,9-diene-2,8-dione; 6-undecyl-5,6-dihydro-2H-pyran-2-one, and phenol, 2,4-di-t-butyl-6-nitro compounds.[76]

Hypoglycaemic (Antidiabetic) Agents

Diabetes mellitus is cohort metabolic syndrome demonstrated by the hyperglycaemic condition in the body. Bitter gourd (Momordica charantia) have been account for the hypoglycaemic polypeptide agents. More than 35 compound were docked against insulin receptor (IR) agonists and antagonist of sodium-glucose cotransporter 1(SGLT1), dipeptidyl peptidase-IV(DPP-IV), and glucose transporter 2 (GLUT2) accordingly for their binding consequences. MOE were opted for the docking analysis.

Numerous peptides viz. LIVA, TSEP, EKAI, LKHA, EALF, VAEK, DFGAS, and EPGGGG were claimed as the promising hypoglycaemic agents either as IR agonist or antagonist of SGLT1, DPP-IV, and GLUT2 lies on their binding consequences through MD. However, experimental synthesis needs to explore as antidiabetic agents.[77]

COVID-19 Inhibitors

COVID-19 pandemic showed the limitation of human being. Still world is lacking of the certain treatment of this calamitous pandemic. Contemporary investigation showed that Mpro protease is account for corona virus replication. Targeting this enzyme prevent the metastasis of corona virus simultaneously and such component could be the reliable candidate of anti-COVID agents. Total seven unidentified molecules were designed to interact with selected COVID-19 proteins. The binding affinity to the Non-structural protein with target NSPs was docked by MD.[78]

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Conclusion

Docking studies still face a significant obstacle because of the flexibility of the receptor, particularly its backbone and the mobility of numerous crucial secondary components that are involved in ligand binding and the catalyst. It is crucial to have a tiny set of models which apply to an enormously huge network since different models produce inconsistent results. MD approach is employed in molecular ranging covers the entire molecule either microscopic or enormous bio molecules; as well as computational chemistry and computer-aided biology. Flexibility factor of ligand and receptor is the challenging issue in front of MD. Recent studies reveal that it has a lot of expectations and opportunities for new drug designing.

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