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Review

Docking profiling and prediction of drug-targets

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Abstract: A computer method called molecular docking forecasts how well ligands will attach to receptor proteins. It has grown into a powerful tool for medication development, notwithstanding its possible use in nutraceutical research. Nutraceuticals are bioactive compounds found in food sources that have potential applications in illness management. Identifying their molecular targets can aid in the development of novel treatments tailored to a given disease. This review's objective was to investigate the use of molecular docking in the investigation of dietary supplements and illness treatment. First, a summary of the basic principles of molecular docking and the different docking software tools was given. Additionally discussed are the drawbacks and challenges of applying molecular docking to nutraceutical research, such as the need for experimental validation and the dependability of scoring functions.

Keywords: Pharmaceutics; docking profiling; target identification; drug-targets

1. Introduction

A computer method for predicting ligands' binding affinities to receptor proteins is called molecular docking. Despite its potential use in nutraceutical research, it has become a powerful tool for medication development. Nutraceuticals are bioactive chemicals found in food sources that can be used to treat illnesses. New treatments tailored to a particular disease can be developed with the aid of their molecular targets. Exploring the use of molecular docking in the research of dietary supplements and disease management was the aim of this review. An introduction to the basic concepts of molecular docking and the range of docking software tools was given first. Molecular docking's drawbacks and challenges in nutraceutical research are also discussed, such as the need for experimental validation and the dependability of scoring functions. Furthermore, the discovery of molecular targets for nutraceuticals in a variety of illness models—such as those for cancer, sickle cell disease, cardiovascular, gastrointestinal, reproductive, and neurological disorders—was emphasized. In order to identify the impact of novel nutraceuticals on disease pathogenesis, we also highlighted biochemical pathways and models from current research that have uncovered molecular mechanisms. Molecular docking is a valuable technique for determining the molecular targets of nutraceuticals in disease management, and this is unquestionably true. It might help in the development of novel treatments and provide details on how nutraceuticals function. As a result, molecular docking has great promise for the development of novel medications to cure illness and has a promising future in nutraceutical research[1-5].

In recent years, molecular docking has emerged as a crucial component of in-silico drug development. This method entails making atomic-level predictions about how a tiny chemical and a protein will interact. This makes it possible for scientists to investigate how tiny compounds, like nutraceuticals, behave within a target protein's binding site and comprehend the basic biochemical mechanism underpinning this interaction. The method is structure-based and necessitates a high-resolution three-dimensional representation of the target protein, which can be acquired using methods such as nuclear magnetic resonance spectroscopy, cryo-electron microscopy, or X-ray crystallography. For molecular docking approaches, a number of free and commercial computational tools and algorithms are available. These tools and systems were created and are now utilized in academic and drug research settings. AutoDock Vina, Discovery Studio, Surflex, AutoDock GOLD, Glide, MCDock, MOE-Dock, FlexX, DOCK, LeDock, rDock, ICM, Cdcker, LigandFit, FRED, and UCSF Dock are among the most widely used docking applications, according to work. The top-ranked options with the highest scores among these programs are AutoDock Vina, Glide, and AutoDock GOLD. Furthermore, depending on the experimental poses1, some of these systems have been successful in predicting Root Mean Square Deviations (RMSDs) between 1.5 and 2 Å1. However, modern docking systems still struggle with flexible receptor docking, particularly receptor backbone flexibility[3-12].

The ligand-receptor complex's computational electrostatics can be examined, screened, and predicted by the docking study. Usually, this investigation is conducted in two separate parts. The first step is to sample ligand conformations based on the active site of the protein. Second, a scoring system is used to rank the conformations. Theoretically, sampling algorithms should replicate experimental binding modes, and a scoring function should be used to score the confirmed results. Compared to in vivo lab investigations, the dry lab approach offers a substantial time and resource investment advantage. As previously mentioned, this method forecasts the orientation of the ligand in a complex that it forms with proteins or enzymes. Additionally, the geometry and electrostatic interaction of the docked complex characterize the interaction. The utility of Molecular Docking in drug discovery and design has been well-established. But there has reportedly been a recent uptick in interest in using this approach in food research. In particular, the molecular targets of nutraceuticals used in disease management are verified through the use of molecular docking.

2. Molecular docking: The goal of molecular docking is to use computer-based techniques to anticipate the ligand-receptor complex. The two primary steps in the docking procedure are using a scoring function and sampling the ligand. Considering their binding mechanism, sampling algorithms assist in determining the ligand's most energetically advantageous conformations within the protein's active region. A score system is then used to rank these confirmations.

2.1. Algorithms: Finding every possible orientation and shape of the protein in combination with the ligand is the main goal of the search method[5, 13-20]. The following categories apply to the search algorithms:

Direct or methodical approach: The following are the three categories of systematic methods:

A. Conformational search: Here, the ligand's structural parameter's torsional (dihedral), translational, and rotational degrees of freedom are progressively altered.

ii. Disintegration In this case, the fragments can either be anchored independently, with the first fragment docked initially and following fragments built outward in steps from that initial bound point, or multiple fragments can be docked during the molecular docking process to build connections between them. It makes use of Flex XTM, DOCK, LUDI, and other tools.

iii. Database Search: Every small molecule that is already listed in the database can have a variety of plausible conformations created using this method, which can then be docked as hard bodies. One example of the tools it use is FLOG.

B. Random methods, often known as stochastic methods, come in three different varieties.

i. Monte Carlo: This method assigns ligands to the receptor binding site at random, scores it, and then creates a new configuration. It makes use of tools like MCDOCK, ICM, and others.

ii. Genetic algorithm: It begins with a population of postures, where the "gene" describes the configuration and placement with respect to the receptor, and the "fitness" is the score. To create the following generation and repeat the agreement, carry out transformations, hybrids, etc. of the fittest. It makes use of AutoDock, GOLD, and other tools.

C. Tabu search: By prohibiting the previously revealed regions of the ligands' conformational space from being reexamined, Tabu search works by imposing notable restrictions that make it easier to investigate a novel configuration. It makes use of Molegro Virtual Docker (MVD)TM, PRO LEADS, and other technologies.

2.2. Scoring: Virtual screening helps determine which ligand structure and rotation is most beneficial with regard to the receptor (protein) by evaluating ligands based on their binding affinity. The scoring function is mostly composed of four groups.

Force field-based: To calculate the binding affinity, it includes the contribution of non-bonded interactions such as hydrogen bonds, van der Waal forces, and Columbic electrostatics in addition to bond-like angle bonding and torsional deviation. AutoDock, DOCK, GoldScore, and other tools are used.

Empirical function: It uses protein–ligand complexes with known binding affinities that have functional groups and some kind of interaction to perform repeated linear relapse analysis on a prepared set of complex structures. Examples include the salt scaffold, the stacking of aromatic rings, the N–O hydrogen link, the O–O hydrogen bond, etc. It makes use of technologies like LUDI score, ChemScore, AutoDock scoring, etc.

Knowledge-based: It gives elements, atoms, and functional groupings the ability to be separated into ward pairs by statistically evaluating a variety of complicated structures. Tools such as PMF and DrugScore are used.

Consensus: In essence, it combines the assessments or orders obtained using several evaluation techniques in different configurations.

2.3. Software: For the virtual screening of phytochemicals or nutraceuticals as potential medicinal molecules, molecular docking has proven essential in many drug discovery efforts. In the middle of the 1980s, the first docking program was created, and efforts to improve docking computations are ongoing. The latest advancements in docking techniques determine the natural substrates of an enzyme in order to predict its capacity. Finding that the protein of interest is a member of a particular superfamily allows for the successful prediction of protein complexes by focusing the search for likely substrates and reaction types within that area.

AutoDock: The Scripps Research Institute created the popular molecular docking program Autodock. Both stiff and flexible docking can be done using this free, open-source program. Autodock optimizes ligand distribution within a

receptor binding site using a Lamarckian genetic method. It also has a number of scoring features to assess how well ligands bind to receptors. PDB, MOL2, and SDF are just a few of the input file types that Autodock supports.
Dock: A molecular docking program called Dock was created by the Chimera team at UCSF. It is an easy-to-use tool for docking tiny compounds into receptor-binding sites. Dock assesses ligand-receptor binding affinities using a grid-based methodology. In order to rank the poses produced during the docking process, it also has scoring mechanisms. PDB, MOL2, and SDF are among the input file types that the dock supports.
ArgusLab: Mark Thomson of the Department of Energy at Pacific Northwest National Laboratory in the USA developed the molecular modeling program Argus Lab, which models solvent effects by combining algorithms from quantum mechanics and classical mechanics. This software can do things like molecular modeling, drug design, and graphic production.
Discovery studio: Dassault Systèmes BIOVIA created the molecular modeling and simulation software program Discovery Studio. A variety of tools for protein modeling, virtual screening, molecular docking, and molecular dynamics simulation analysis are included. The molecular docking component is used to evaluate the intensity of the contact between a ligand (small molecule) and a target protein, as well as to forecast the mechanism of binding. A range of docking algorithms, including CDOCKER, GOLD, and LibDock, are used by Discovery Studio to provide a set of potential ligand binding poses and rank them according to their anticipated binding energies. Additionally, the software offers capabilities for comparing the binding modes of several ligands to the same protein target as well as for displaying and analyzing the docking results.
CB-DOCK2: A better version of the CB-Dock server for protein-ligand blind docking, CB-Dock2 combines homologous template fitting, cavity detection, and docking.

2.4. Active site prediction: Both initial specification and post-docking identification of the binding pockets are possible during molecular docking[21-24]. As a result, three distinct methods can be thought of to confirm the binding pocket of interest during molecular docking, as indicated below.

a. Docking site-directed: Here, dock the ligand after determining the protein–ligand interaction site.
b. Blind docking: Without being aware of the binding site beforehand, the docked ligand is right onto the entire receptor structure in this instance.
c. Docking using a typical standard: In this case, the protein is docked with the typical small molecule or ligands. It is easier to estimate the appropriate binding pocket when using the standard ligand.

3. Applications of molecular docking: Molecular docking is widely used for basic science application and research purpose[11, 25-37]. Here, we highlighted some of the common applications:
Hit identification/virtual screening: In drug discovery, molecular docking is frequently utilized for hit identification. By forecasting the binding affinity of small compounds to a protein or receptor of interest, it aids in the identification of possible therapeutic candidates. A huge database of small compounds can be screened via docking to find those that have a high affinity for binding to a target protein.
Lead optimization: Using molecular docking, the structure of a hit chemical can be optimized to increase its binding affinity and selectivity. By forecasting the binding patterns of altered structures, docking can also be utilized to create novel analogs.
Bioremediation: To forecast the binding affinity of small compounds to enzymes involved in the breakdown of environmental contaminants, bioremediation uses molecular docking. Designing inhibitors or activators of these enzymes to improve the effectiveness of bioremediation can be aided by docking.
Clarification of structure: Proteins with unknown structures can also have their structures clarified through the use of molecular docking. Docking can be used to anticipate how tiny molecules will bind to proteins and, based on that prediction, create a homology model of the protein. An accurate protein structure can subsequently be obtained by refining the produced model using experimental data.
In-silico drug property prediction: The Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) characteristics of small compounds can also be predicted via docking. Early in the drug development process, molecules with undesirable qualities can be filtered out using the expected ADMET attributes. AutoDock Vina, GOLD (Genetic Optimization for Ligand Docking), Glide, and Schrödinger Suite are a few noteworthy examples. These software programs offer sophisticated algorithms and computational methods for effective ligand-receptor docking simulations, which enable the identification of possible therapeutic candidates and the prediction of binding affinities. Additionally, they use ADMET prediction modules, which allow evaluation of the drug's behavior concerning absorption, distribution, metabolism, excretion, and possible toxicity.

4. Conclusions and future perspectives: One helpful method for determining the molecular targets of nutraceuticals used in disease treatment is molecular docking. It makes it possible to estimate the binding affinity and conformation of nutraceuticals with target proteins, which can be used to discover potential therapeutic targets. Molecular docking is now an essential tool in the drug development process due to the availability of databases and advancements in computational tools. By reducing the time and cost required for traditional experimental procedures, the use of this

technology has increased the efficiency and efficacy of drug development. Consequently, the application of molecular docking in dietary supplement research has significant promise for the discovery of new therapeutic targets as well as the development of safe and effective dietary supplements for illness treatment. A powerful method for determining the molecular targets of nutraceuticals used to treat disease is molecular docking. Finding potential nutraceutical targets will become more accurate and efficient with the advancement of molecular docking techniques and algorithms. The complex interactions between nutraceuticals and their molecular targets will also be better understood by combining molecular docking with other computational methods like network analysis and machine learning. Furthermore, personalized medicine will be able to create personalized treatment plans based on an individual's genetic composition and disease state thanks to the application of molecular docking.

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