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PHARMACEUTICAL APPLICATION OF MOLECULAR DOCKING IN DRUGS, OPTIMIZATION, CHARACTERIZATION AND SYNTHESIS

Zaid Noor Obaid Al-Husseini[1]* and Ban Zaidan Neema[2]

[1]Babylon Adminstration of Education.

[2]Karbalaa Adminstration of Education.

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***Corresponding Author**
Zaid Noor Obaid Al-Husseini
Babylon Adminstration of Education.

ABSTRACT

Molecular docking is based on method related with silico structure-based commonly utilized discover of drug. Docking support the consistency of novel drugs of important therapeutic to control many disease, at a molecular level MD suitable for predicting ligand-target interactions. MD was firstly developed to explain understanding molecular recognition mechanisms between molecules in small and large size. In this review we explain role of MD in evaluation, characterization, determine the efficacy of some new compound against covid-19 using this technique by ACE2 receptor.

INTRODUCTION

Molecular docking (MD) is modeling of a kind of bioinformatics which include two or more molecules that interact to yield the constant adduct. Depending upon properties attached of ligand and target, it foretell the Tid -dimensional structure of any complex.[1,2] MD creates Varient imagable, structures of adduct that are together grouped and ranked utilizing function of scoring in the software.[3] Docking imitation forettel conformer of optimized docked according to system total energy.[4] Despite to all prospect approaches, chemistry ligand, flexibility of receptor and function scoring yet remained the challenge.[5] Medicinal chemists can now riddle compounds of hundreds of thousands of in an array of receptor molecules and putative drug targets.[6][7] Un necessary to say, docking molecular comes in many shapes and sizes, allowing the researcher to balance speed and thoroughness in the computation. MD is an magical scaffold to understood interactions drugbiomolecular for the discovery and reasonable drug design, as well as in the mechanistic study by development a drug into the suitable receptor binding site specially in a non-covalent manner to compose Stable complex

for Possibilities effectiveness and more Definition.[7,8] The obtained information can be used in the docking technique to suggest the binding energy, free energy and stability of the complexes.[1] More recently, the docking technique for temporary binding potentials of a pre-blind receptor complex is applied.[9,10] The perfect Practical application of MD needed to a data bank of suitable target search in PDB format and preparation of a PDB ligand file. To perform this process easily, many programs are available (Discovery studio, etc.). On the other hand, these tools provide suitable ligands depending on their ability to interact with target proteins such as DNA. Molecular binding of small molecules to the appropriate target includes selection of pre-determined models of the potential conformation of the linker in the specific groove of the target for the purpose of forming the optimal conformation of the complex. This can be easily done using the recording function of the program.[11,12] Infrared spectroscopy, nuclear magnetic resonance (NMR) spectroscopy, and X-ray crystallography are techniques to investigate and create 3D structures of any organic molecule/biomolecular targets.[13] Finally, homology modeling can make the determination of the unknown structure structure of proteins with high sequence similarity to the known structure. This provides an alternative approach to establishing the target structure, which is a starting point for the discovery of multiple drugs and to reduce the cost spent on the rest of the initial tests.[13]

Docking types

Inclusive used tools of the docking appoint search algorithms like, algorithms based fragment, algorithm of genetic and dynamics algorithms of molecular. Besides this, there are many tools like as, GOLD, FlexX, DOCK and ICM, which are essentialy emploied for high throughput docking imitation.[14,15] There are different kinds of procedures in MD including either ligand/target flexible figure(1).

There are two distinct forms of docking.

1. Rigid docking
2. Flexible docking

Assuming the inelasticity of the compounds, the best match with the other compounds in the scoring system parameters should be produced by rearranging one of the compounds in a three-dimensional space. The bonding form can be formed with or without the receptor binding activity. In coupling with conversion, we correct molecular flexibility to recognize confirmations for the ligand molecules with receptor as they exist in the complex.[16]

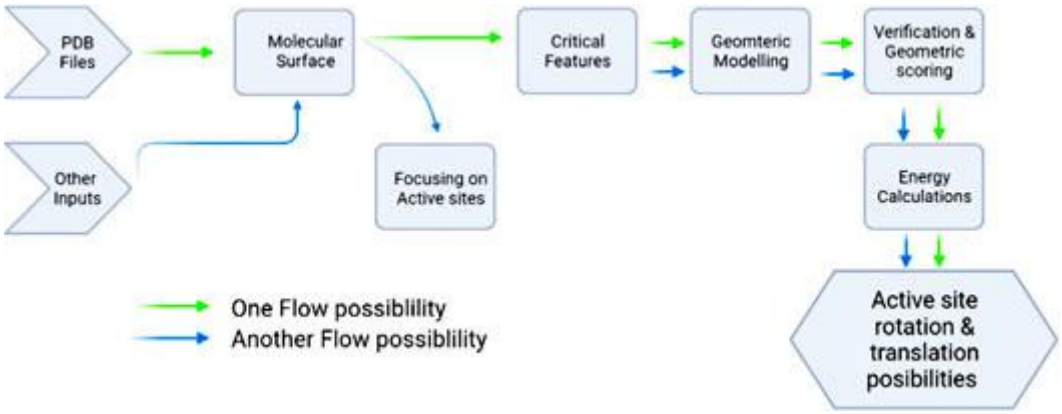

Figure 1: Refer Rigid and Flexible docking.

Models of molecular docking

Discovered the "lock-and-key method" in 1890, as seen in figure 2, to explain how biological processes work. inserted of 4 A substrate is into the active site of a receptor in the same rout as a key is inserted into a lock. In figure 2, biological locks appear special stereochemical property that are wanted for their operation.[17]

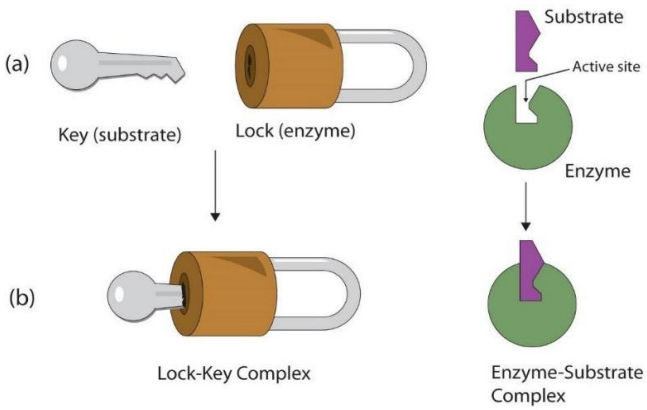

Figure 2: Emil Fischer theory.

Softwares available for molecular docking

Molecular docking methodology search the attach molecules in small size like drugs with a target protein in specific binding site. As more structures of protein are experimentally set using nuclear magnetic resonance (NMR), X-ray crystallography or spectroscopy, molecular docking is progressing used in drug discovery tools.[2] Morever, when proteins whose structures are not identified by docking versus homology-modeled targets,[18] With the strategies available in docking, the druggability of the compounds and their specificity against a particular target can be calculated for further lead optimization processes. Program molecular docking perform bya searching algorithm in which the ligand conformation was evaluated recursively till the convergence to the lower energy is reached.[19] Finally, score

function ffinity, ΔG [U total in kcal/mol], is used to rank the candidate poses as the sumation of van der Waals with electrostatic energies. The specific interactions in biological systems leading resulting forces aimed toward complementarities between electrostatics of the binding site surfaces, shape and the ligand or substrate.[20] Recently, the use of protein bonding programs has increased more stubbornly compared to previous years and past decades, due to the increase in development and reduction in costs.[21] Below is a list of the most popular software, producing organizations or institutions, a brief description, web service availability and licensing, https://en.wikipedia.org/wiki/List_of_protein-ligand_docking_software.

Molecular docking in modern drug discovery: Principles and Recent applications

Molecular fusion programs have been improved and developed for many years, although their ability to produce a drug that is compatible with drug action within the body is still limited and generally questionable.[22,23] Below we will present the idea and usefulness of the docking approach to identify the active outcomes of a variety of different receptors/targets.

HIV 1 Integrase—a site of new binding for AIDS drugs was discovered by number of authors, using docking while considering the receptor flexibility via molecular dynamics. The group employed for AutoDock in conjunction with method relaxed-complex to find novel style of inhibition of HIV integrase.[24]

Binding of hydroxytyosol with HIV integrase

Candidate natural substances for COVID-19 therapy

In the next We'll address, we'll review some of the most important natural substances that could be used to treat 2019-nCoV infection in the following session.[25]

Using docking for Candidate natural COVID-19 therapy

In the next We'll address, we'll review some of the most important natural substances that could be used to treat 2019-nCoV infection in the following session. ACE2 is the receptor of the newly emerging 2019-nCoV receptor,[26] Since this host cell receptor is required for viral entry, blocking ACE2 aids in the prevention of 2019-nCoV infection. It could really take several years to discover and synthesize new medications to target ACE2 and treat 2019-nCoV, and the safety of new therapies may be a substantial impediment that demands so much time to evaluate. Whenever a result, as the disease worsens, it is problematic to establish and test compatibility, safety, and toxicity of new drugs in such a short span of time.[27]

Importantly, in this brief review, we breif the efficacy compounds of plant source that could be ACE2 targeted for 2019-nCoV medical care. Interestingly, we recommend plausible drugs that target the receptor ACE2 and has anti-virus influence to restrict 2019-nCoV illness using MD, including baicalin, and hesperetin) (Figure 3,4) respectively.

Hesperetin

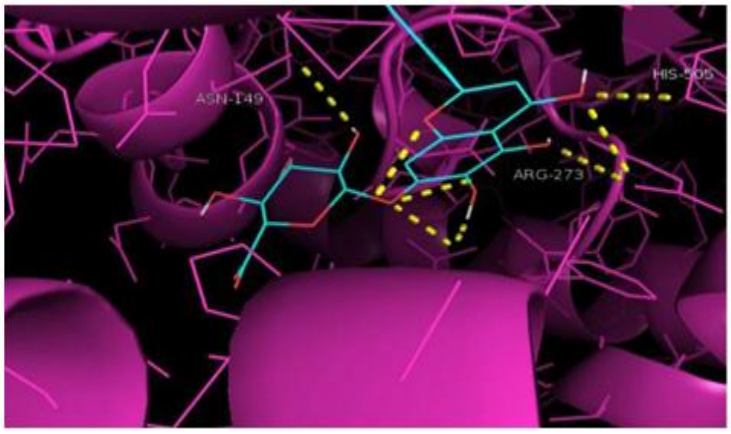

Figure 3: The docking result from baicalin to the ACE2 enzyme (Chen and Du, 2020).

Hesperetin is a flavanone that is derived from eriodictyol with 4'-methoxy. Hesperidin with dose-dependent suppressed the SARS-coronavirus in cell line. Furthermore, though the MD of hesperetin to the angiotensin convertinf enzyme, some fragrances have indicated that hesperetin might block ACE2, and the data have set that hesperetin has a possible binding with ACE2.

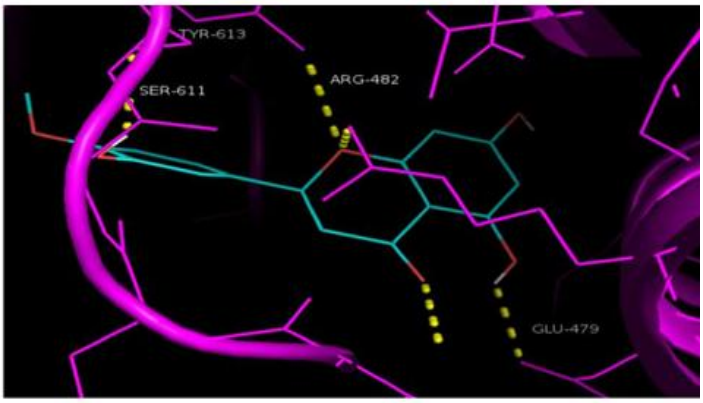

Figure 4: The molecular docking performance of the Hesperetinto ACE2 enzyme was evaluated.[9]

CONCLUSIONS

From this study we concluded that MD very suitable technique for evaluate therapeutic efficacy of new drugs or new therapeutic aspect of any drugs or active compound using specific pathway or receptor specially very difficult control disease such as COVID-19.

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