IJPSR (2023), Volume 14, Issue 4 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 July 2022; received in revised form, 01 September 2022; accepted, 20 October 2022; published 01 April 2023

MOLECULAR DOCKING IS AN IDEAL TOOL IN PHARMACEUTICAL DRUG DEVELOPMENT OF ANTI-TUBERCULOSIS MOLECULES

Fathima Asra [1], Naresh Dumala [*1], Fathima Ajra [2], Shaik Mallika [3] and Kannan Vadivel [4]

Koneru Lakshmaiah Education Foundation [1], Vaddeswaram, Guntur - 522502, Andhra Pradesh, India.
Nimra Institute of Medical Sciences [2], Nimra Nagar, Ibrahimpatnam, Jupudi, Vijaywada - 521456, Andhra Pradesh, India.
Marri Laxman Reddy Institute of Pharmacy [3], Dundigal - 500043, Hyderabad, Telangana, India.
Smt. Gandhimathi College of Pharmacy [4], Nallanpillaipetral, Tiruvannamalai - 606808, Tamil Nadu, India.

Keywords:

Tuberculosis, Drug-resistance, *Mycobacterium tuberculosis*, Bioinformatics software, Molecular Docking, Docking tools, Genomics, Proteomics, AutoDock, Drug discovery

Correspondence to Author:
Dr. Naresh Dumala

Professor,
Koneru Lakshmaiah Education Foundation, Vaddeswaram, Guntur - 522502, Andhra Pradesh, India.

E-mail: nareshpharma2020@gmail.com

ABSTRACT: Advancements in X-ray crystallography, Nuclear magnetic resonance (NMR) spectroscopy, and innovation projects like the human genome project left gigantic amounts of biological information accessible to the common public, academicians, and industries. Computer-Aided Drug Design (CADD), such as molecular docking, is an ideal method to exploit this biological information in rapid drug development and discovery. The basic principle of molecular docking is explained in the present review, with a brief introduction to bioinformatics and Mycobacterium tuberculosis. Methodology and types of molecular docking are also described along with various software and programs used *viz.* AutoDock, FRED, FlexX and GOLD. Further, two fundamental wings of molecular docking techniques *i.e.*, searching algorithms and scoring functions, are briefed. Molecular docking tools are discussed as their applications in the anti-tuberculosis drug discovery process. Drug molecules targeting various cellular enzymes important for the viability of multi-drug resistant *M. tuberculosis* studied using *in-silico* docking methods are reviewed. In contrast to high-throughput screening, molecular docking methods speed up the drug discovery process. It has been concluded that molecular docking studies significantly take part in novel drug development by rapid virtual screening of existing drug databases and in the discovery of new drugs which are fundamental to pharmaceutical industries and medical science to overcome the emergencies situations like the emergence of drug resistance in medical pathogens and changing disease scenarios.

INTRODUCTION: Extensive research in biological science generated a gigantic amount of scientific information related to genomics, proteomics, metabolomics, drug-target interactions, *etc*.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(4).1534-46

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.14(4).1534-46

Managing such huge scientific information manually has become a challenging task. For instance, the DNA sequence obtained from the human genome project, if printed, may need approximately 100 volumes of telephone dictionary to demonstrate the whole genomic information [1].

Hence, exploiting this scientific information for human applications is only feasible by adopting automated techniques. Bioinformatics is a field of life science that uses the computer for the computation of biological information, and it is also referred to as computation biology.

It is an interdisciplinary arena that enables the exploration of a huge amount of biological data by storing, organizing, annotating, systematizing, mining, interpreting, and understanding the complex volumes of scientific data as shown in **Fig. 1**. The field utilizes modern, conventional computer science, mathematics, statistics, cloud computing, machine learning, folding algorithms / molecular modeling, iterative and simulation approaches [2].

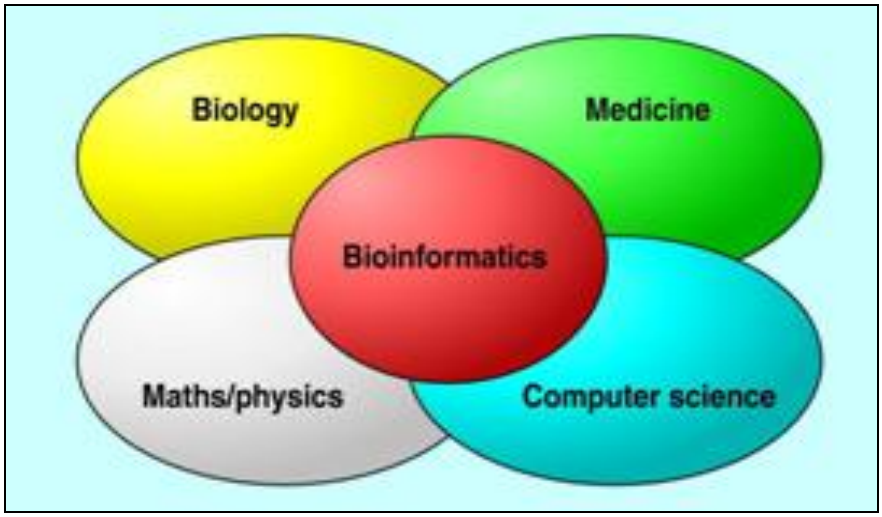

FIG. 1: EMERGENCE OF BIOINFORMATICS FROM THE CONVERGENCE OF VARIOUS FIELDS OF SCIENCE [3]

Important bioinformatics tools mainly include an internet facility and computer software programs, mostly available on public websites. The basic activity of bioinformatics includes analysis of DNA sequences and proteins with the help of the World Wide Web available software programs and databases[3]. The computer programs and software developed are used to handle much biological information on genome (DNA, RNA), metabolites, and proteins. These bioinformatics tools also have immense applications, as indicated in **Fig 2.**

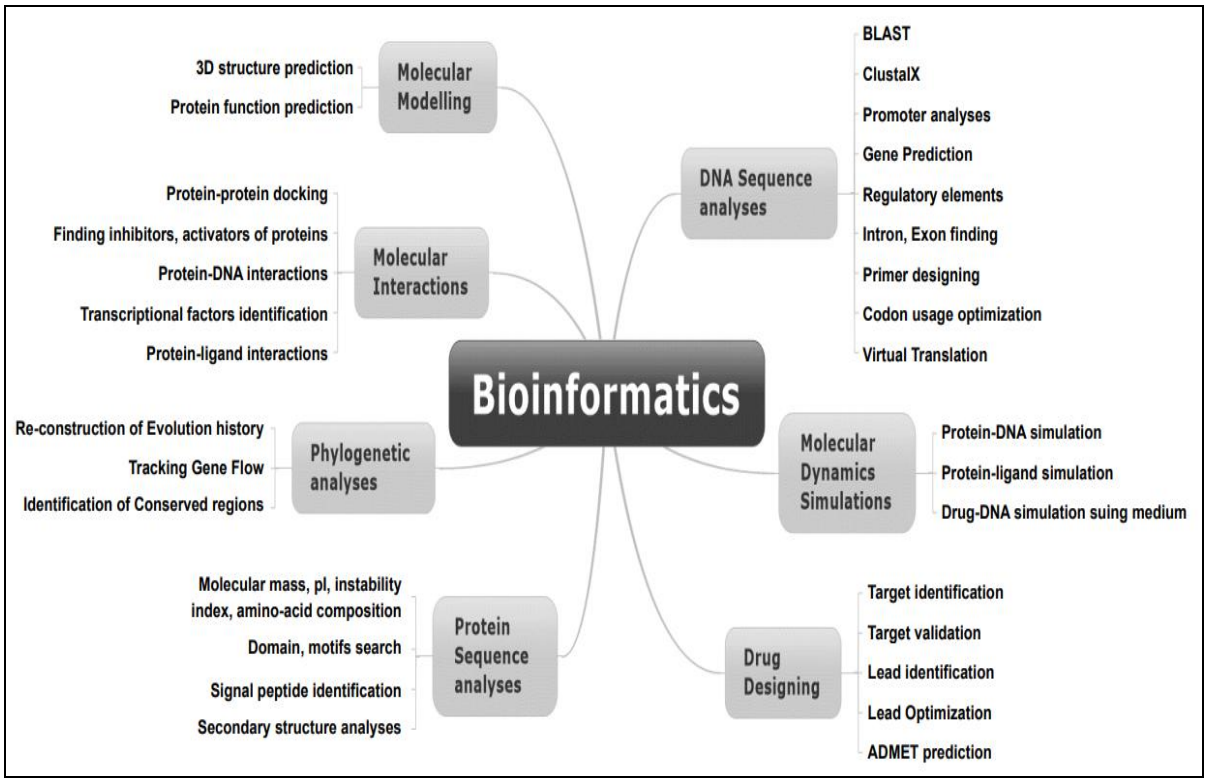

FIG. 2: BIOINFORMATICS APPLICATIONS IN DIFFERENT FIELDS OF BIOLOGICAL SCIENCES [4]

As far as applications for computational biology or bioinformatics in drug discovery and design is concerned, it is a key component that saves researchers time and reduces the cost of research [5]. Since, drug isolation and characterization is dated back to ancient times, tremendous traditional and advanced research in this area accumulated a huge drug database. Today, the count of pure drugs with known structures has touched near tens of millions, and this massive data is fundamental for drug development and research. Scrutinizing such a huge drug depository employing traditional experimental models and pharmacology is enormously expensive and time-consuming.

The CADD (computer-aided drug design)tool of bioinformatics plays a substantial role in drug design, and development of drug leads through computer-mediated simulation, prediction, and determination of ligand (drugs) and target (receptor) interactions as a majority of biochemical processed in living organisms rely on the interactions of ligand and proteins. This computational technique being an important tool in drug research and development, critically enhances the rate of successful drug screening, avoids blindness research, and is more economical and less time-consuming [6, 7]. Molecular docking is a computational method used for studying ligand and target protein fitness at the atomic level. The method is one of the significant tools in drug discovery, which enables the prediction of the small molecule behavior at the active site of targeted proteins and the understanding of the basis of biochemical reactions.

Mycobacterium tuberculosis is a bacterium that causes a communicable disease, Tuberculosis (TB) by mostly attacking the lungs, followed by other parts of the body in low-income nations. Among the top ten diseases, tuberculosis is one of the leading causes of death over the globe. World Health Organization (WHO) estimates about 1.4 million deaths due to TB, and infection is even more severe in HIV (Human Immunodeficiency Virus) patients [8, 9]. TB is being managed successfully with current medications, but it still poses several threats to the healthcare system. Amidst these, a few are drug resistance TB like XDR-TB (exclusively drug-resistant-TB), MDR-TB (multi-drug resistance-TB), TDR-TB (totally drug-resistant-TB), the risk of diabetes mellitus development in TB patients, and co-morbidities associated with AIDS (Acquired Immunodeficiency Syndrome) patients [10, 11, 12]. Despite intensive anti-TB research in the last 40 years, the existing drugs for TB are found to be less effective and cytotoxic against drug-resistant bacteria [13]. The recent approach to developing the drug candidate against TDR, MDR, and XDR-TB has resulted in the discovery of a limited number of therapeutic agents, such as telacebac or Q203 and TBA-7371, which are potential drugs for the treatment of XDR and MDR-TB [14].

Thus, there is an emergency in developing a potential multi-targeting drug that can bind to different biological targets. Since the approach targets different protein targets, modern techniques like molecular docking methods intensify the processes by advancing the prediction of these possible drug-binding targets in contrast to traditional methods. Present review focus on the detailed discussion of molecular docking techniques for drug discovery with special emphasis on drug development using bioinformatics tools concerning anti-TB molecules.

Molecular Docking and its Principle: The interaction of protein-protein and protein to small molecules are fundamental to the existence of life through the production of energy and biomass. Biochemical processes anticipating anabolic and catabolic pathways form a metabolic network mediated through the interaction of enzymes (protein target) and substrate (ligand). During the disease, these interactions are often dysregulated. The protein-protein interaction presents both inside and outside the cells is an important target for therapeutic agents [15]. Hence, protein-to-protein interactions are important regulatory events in physiology and pathology that are critical targets for small molecules in the drug development process [16]. However, proper orientation of protein(s) and ligands is essential for interactions to take place, which can be achieved by using advanced molecular docking techniques. Hence, molecular docking is a technique to determine the appropriate orientation of ligands and target proteins using the computational method to determine the proper ligand fit with the receptor [17]. Accurate orientation of ligand-protein is

accomplished by scoring functions that indicate the proper fit of ligand into the target protein's site both geometrically and energetically [18]. Molecular docking involves two interrelated steps: ligand sampling conformation in the protein target site, i.e., active site, and grading ligands conformation based on scoring function [19]. On the other hand, the ligand binding conformations are predicted using search algorithms and the binding energies (7 - 10 kJ/mol) between protein and ligand docking are predicted through scoring functions [20]. The basic principle of molecular docking can be explained better through Fisher's Lock-Key model introduced in 1894, shown in **Fig. 3**. The model proposes that the protein and ligand, via energy matching and geometric matching, could identify each other[21]. In this model, both ligand and protein are considered rigid structures where no change in the structure of receptor proteins is expected. This limitation of the Lock-Key model was instigated in the proposal of Induced Fit Theory, which suggests that during docking studies, the structure of ligands and proteins are considered flexible [22]. The theory was validated by applying it to the drug-protein interactions resulting in more accurate results.

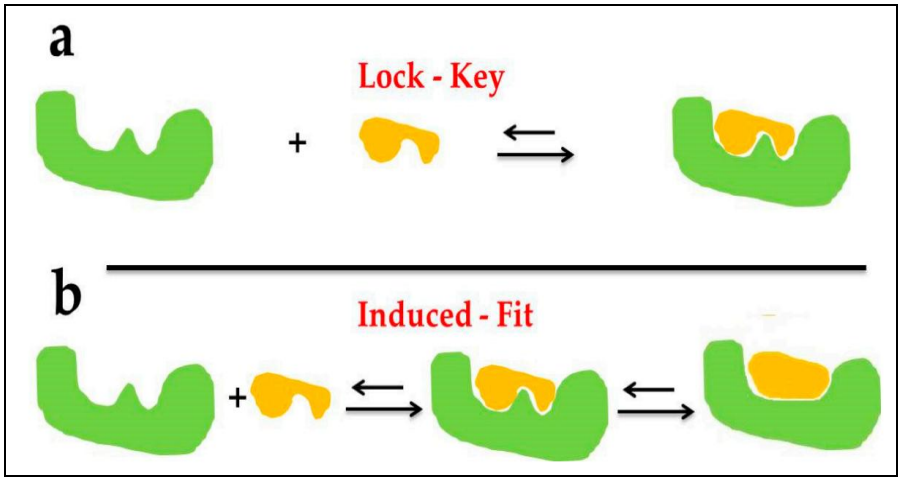

FIG. 3: COMPARISON OF PROTEIN CONFORMATION IN LOCK AND KEY MODEL (A) AND INDUCED-FIT THEORY (B) [23]

The various types of interaction forces or energy that mediate ligand and proteins interaction include Electrodynamics forces or Van der Waals interaction energy, electrostatic forces or Electrostatic interaction energy, steric forces or solvation change the energy and hydrophilic and hydrophobic interactions, and covalent bond [24, 25, 26].

Workflow of the Molecular Docking: The main objective of molecular docking is to analyze ligands for proper orientation or conformation (also called "pose") so they can bind to a protein target. Therefore docking protocol consists of two steps; sampling conformation of ligand that can bind to the active site of the protein target using searching algorithms and assigning as the core for ligand conformations via scoring functions [27]. Searching algorithms generate several conformations, including the experimentally binding mode assigned to the highest score by scoring functions. Some search algorithms include Monte Carlo, Fragment-based, Point complementary, distance geometry, systematic searches, *etc* [28, 29]. The primary requirement of molecular docking studies is to retrieve 3D structures of both ligand and target macromolecules *viz.*, protein, DNA, or RNA, from online available data banks. The 3D structures of macromolecules are obtained from PDB (Protein Data Bank) [30, 31]. Meanwhile, the structures of ligands are retrieved from various resources like Pub Chem and ZINC, and they can also be obtained by drawing the Chem Sketch tool. Therefore, the steps mentioned below are the major ones involved in docking.

Preparation of Target Protein: as described, the 3D structure of proteins obtained from PDB is pre-processed based on the parameters available to form the stable ligand-protein complex. These protein preparations include optimization of hydrogen bonds, addition/removal of hydrogen bonds, elimination of atomic clashes, water removal from protein cavity, the addition of side

chain, missing residue fillings and charges stabilization [32].

Prediction of Protein (Target) Active Site: active site of the protein is directly anticipated in the binding with ligand to from ligand-protein complex. Hence, before docking, this active site is predicted by its modification, like removing heteroatoms and water molecules. The receptor might possess many active sites in which the appropriate one can be chosen [33].

Preparation of Ligand: ligands obtained from different databases must be prepared to get conformation that can bind to the receptor. Ligand's pre-preparation should be according to the "Lipinsky's Rule of 5" in order [34].

The rule proposes that the drug possesses more than 5 hydrogen bond donors and 10 hydrogen bond acceptors with CLog P >5.0 (calculated Log P), and a molecular mass of more than 500 is more likely to get adsorb and permeate. The rule is used to identify the difference between drug-like and non-drug-like molecules.

Molecular Docking: The ligand with different conformations is docked with the protein target's active site, and their interaction is analyzed. The scoring function assigns the score for the best ligand-protein complex docked and refers to **Fig. 4**.

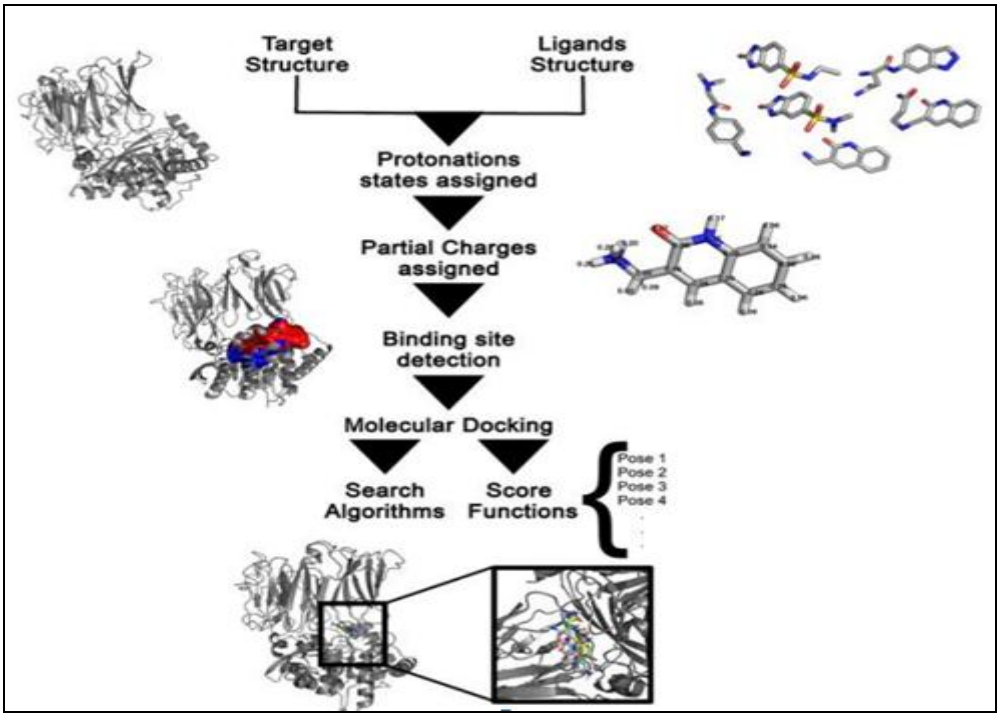

FIG. 4: MOLECULAR DOCKING PROCEDURES FOR DOCKING SCORE CALCULATION TO OPT FOR BEST LIGAND-PROTEIN COMPLEX [35]

Though, if such a situation arises where the 3D structure is not available for few protein, the 3D structure of these proteins can be obtained using computational prediction methods *viz.*, ab initio, prediction and comparative modelling [27]. Similarly, the 3D structure of the ligand is not found after the virtual screening, it can be obtained from the 2D structure with the help of software Concord, Avogadro, Chem Draw, Chem Sketch, *etc* [36, 37].

Software Available for Molecular Docking: Two important sections of molecular docking are search algorithms and scoring functions accountable for the prediction of the ligand conformation and assigning scores for the ideal ligand-target complex, respectively, using computational techniques, and together these functions accomplish the molecular docking process [38]. The detailed discussion of search algorithms, scoring functions, and their corresponding available software are explained below.

Search Algorithms: these algorithms predict the ligand conformation or orientation, also known as posing [39]. Search algorithms should be able to generate the optimum number of ligand

orientations that is useful in practically determining binding modes. Considering the internal and roto-translational degree of freedom, these algorithms analyze and generate the ligand conformation (pose) at the protein target site [30]. Several search algorithms used in molecular docking studies are listed in **Table 1**. Search approaches are further categorized as deterministic, stochastic, and systematic search algorithms. Deterministic search utilizes the previous state in the determination of conformation and orientation of ligand in each iteration and compares it to the previous one; the new state has a lower or equal energy value. But, the cost of computation is higher in this type of algorithm. Sometimes it results in the trapping of ligand conformation unenviably to a local energy minimum [40, 41].

Simulations of molecular dynamics and methods of energy minimization are a few examples of this kind of algorithm. Through the Stochastic search algorithm, the degree of freedom of the ligand can be changed randomly without promising convergence to the ideal solution, and it can be improved by conducting an iterative process. Evolutionary algorithms, Monte Carlo, Swarm Optimization, and Tabu Search are some commonly implemented stochastic search algorithms [41]. The systematic search algorithm uses the degree of freedom of each ligand incrementally, and with increased free rotational bonds, there will be an increased number of evaluations experiencing combinatorial explosion. These search algorithms are further sub-categorized into the combinatorial ensemble, incremental and exhaustive construction [40, 41, 42].

Scoring Functions: Soon after the thousands of ligand conformation are predicted, they are raked using scoring functions. The scoring is based on the free energy, qualitative numerical measures of binding energy, and interactions energies [43]. Scoring functions are classified into different types based on classical force-field, empirical, and knowledge.

Classical Force-flied-based Scoring Functions: this scoring function measures binding energy by determining the sum of non-bonded interactions, including vander Waals and electrostatic forces. For the calculation of binding energy, in a few algorithms, parameters like hydrogen bonds, salvations, and entropy contributions are taken into consideration [44]. Coulombic formulation and Lennard-Jones potential function are used to calculate the electrostatic and vander Waals terms, respectively. Such calculation provides information about protein environment modeling based on charge-charge interaction and acceptability of the close contact of protein-ligand [45, 46]. This scoring function can be further refined in docking studies using techniques like free-energy perturbation methods (FEP) and linear interaction energy [47, 48]. These functions are low-speed computational methods that also decline the precision of the long-range bonding effect. The effect of entropies and solvents is neglected in this type of function [40]. The example for this kind of function employs the DockThor program to predict a pose.

Empirical Scoring Functions: these functions are idealized by Hansh and Fujita and are derivative of the quantitative structure-activity relationship [40]. The main objective is to predict high-precision binding affinity with the help of well-understood investigational data on binding affinity [41]. These functions have simple energy terms to calculate. Some of the empirical scoring functions include Glide score and Chemscore. In these functions, various energy components like hydrophobic effect, ionic interactions, and hydrogen bind together to contribute the binding energy. Different software is used to treat each term differently in these functions, and even in different algorithms, the number of terms included is also different [49].

Knowledge-based Scoring Functions: this function is computationally simple and mainly used to screen large molecule databases. The atom pair's interactions frequency noticed in practically determining 3D ligand-target complexes is fundamental to this type of scoring function. Some examples of this category of functions include PMF and FlexX program DrugScore [40, 41]. Calculating the score is done by considering penalizing revolting interactions between protein and each ligand atom and preferring selected contacts within recommended cutoff. Consensus scoring is an advanced method in docking analysis that predicts the docking conformation by combining different scores. The acceptance criteria of a potential binder

or ligand pose are only possible when it attains a good score under several scoring strategies [50].

Types of Docking Methods: Docking methodologies are categorized into several types based on the structure of ligand and proteins target (receptors).

Rigid Molecular Docking (Both Ligand and Protein are Rigid Structure): in this type of docking, protein and ligand are considered fixed in their spatial orientation and only the posture and spatial position of two molecules will change[51]. The search space in this kind of docking is restricted taking account of three rotational and translational degrees of freedom.

Through this docking, a huge number of ligand conformations are created with suitable surface complementarity and re-ranked with the help of free energy of approximation. The docking technique is simple in calculation amount as well as calculation difficulty; hence is more useful in macromolecule docking methods like protein-nucleic acid and protein-protein complexes. The docking method was successfully applied in maltose-protein docking simulation by binary docking technique [52]. The docking tool MEGADOCK, identical to ZDOCK is used to produce docking conformations that generate docking conformations using Fast Fourier Transform (FFT) in a grid-based 3D space. However, calculations in contrast to ZDOCK are 8.8 times greater as the score functions are simpler where only electrostatic and shape complementarities are taken into account [53].

TABLE 1: BIOINFORMATICS SOFTWARE USED IN MOLECULAR DOCKING STUDIES

Software	Features & Applications	Search Algorithm	Scoring function	Designed company
AutoDock [54]	Rigid-Flexible docking; Used in the analysis of ligand covalent-bound	Lamarckian Genetic Algorithm (LGA) Genetic algorithm (GA)	Force-field methods	D. S. Good sell and A. J. Olson The Scripps Research Institute
FlexX [28, 55]	Rigid-Flexible docking; easy operation, high efficiency, rapid speed docking, suitable for small molecule virtual screening	Fragmentation algorithm	PLP, Drug Score Screen Score, Flex X Score,	M. Rarey Bio Solve IT and T. Lengauer
DOCK[56, 57]	Flexible ligand-receptor docking; Step-by-step geometric matching strategy	Fragmentation algorithm	GB/SA solvation scoring, Chem Score, other	I. Kuntz University of California, San Francisco
	Flexible docking; utilized for virtual screening of database, evaluated for reliability & accuracy in the docking simulation	Genetic algorithm (GA)	Chem Score, Gold Score	Crystallographic Data Centre, Cambridge
FRED [58]	Rigid body Docking; In protein active site possible conformations are examined by a Nonstochastic approach	Shape fitting (Gaussian)	PLP, Screen Score, Gaussian shape score, user define	Open Eye Scientific Software
Glide [59]	Flexible docking; High throughput virtual filter, standard precision, extra precision search algorithms are fundamental to the Docking program	Exhaustive systematic search	Glide Comp, Glide Score	Schrödinger Inc.
LigandFit[60]	Shape-directed rapid docking; Good hit rates are generated using Lig Score	Monte Carlo Sampling	PMF, PLP, Lig Score	Accelrys Inc.

Note: GOLD; Genetic Optimization for Ligand Docking, FRED; Fast Rigid Exhaustive Docking

Rigid Protein and Flexible Ligand Docking (Semi-flexible Docking): To overcome the difficulty of docking where both ligand and target are considered flexible which is costly and energy perfect-fit complex is minimum semi-flexible docking approach is used to balance between computational time and accuracy. This methodology is adopted by the majority of the programs like Dock, FlexX, and AutoDock [61, 62]. During the calculation process of semi-flexible docking, receptor protein conformation is maintained, and non-critical parts like bond angle and length are changed. Due to the model's prediction and calculation ability, the method is extensively used in macromolecules (enzymes, nucleic acid, proteins) and small-molecule docking

simulation [42]. AMBER force field *viz.*, desolvation, conformational entropy, hydrogen bonds, vander Waals, and electrostatic interactions based scoring function is used in this docking method. The empirical scaling factor acquired from the investigational database is used to weigh each of these terms. Using AutoDock 4.0 the protein-protein interaction docking interactions can be evaluated, and the latest version for virtual screening and molecular docking is AutoDock Vina [63].

Flexible Molecular Docking (Both Ligand and Receptor are Flexible): The orientation of ligands and receptors freely changed during the calculation of flexible docking. It is a highly accurate docking simulation nearest to the real docking condition, and this method can accurately investigate the recognition between molecules. But, due to variables' geometric growth in terms of the number of atoms, the method is time-consuming, computationally intensive, and needs high-level computer hardware and software system. The most popular software for molecular docking of this kind is FlexX [64].

Docking Tools Available in TB Drug Design: As described above, a continued search for drug molecules in a limited time is essential due to drug resistance and aggressiveness of the TB disease. Isolation of a broad-spectrum potential drug active against TB through experimental trials is very difficult and time-consuming, and the results are less promising. Hence, molecular docking enables rapid screening of molecules from a drug database in isolation of a broad spectrum of potent anti-TB drug molecules. Some of the molecular docking studies involved in the virtual screening of drugs against tuberculosis reported in the literature are discussed here.

Accelrys Discovery Studio 4.0 was used in the molecular docking of indolizines into the target protein's active site, as shown in **Fig. 5**. The mycobacterial enzymes trpD (anthranilate phosphoribosyltransferase) and InhA (enyol-ACP-reductase) X-ray crystal structures with their inhibitor were recovered from PDB (Protein Data Bank). The clean protocol tool is used in preparing crystal complexes. Parameters like atoms names, removal of water molecules, bond order and correct connectivity, ionisable residues protonation at pH 7.4 and addition of missing residues in protein were standardized. The docking protocol was validated by co-crystallization of ligand and de-docking into enzyme's active site to ensure proper binding site definition and evaluate docking algorithm accuracy in generating co-crystallized ligand pose. Ligand conformations are generated by docking the ligand in rigid receptors.

In targeting the active binding site, the optimal ligand pose was ensured by using extra scoring functions PMF, Jain, PLP1 and PLP2. Their negative score indicatesthe strongest ligand-receptor binding affinity. Docking of indolizines in respective receptor targets and binding energy calculation was conducted using the C-Docker protocol and procedure of *in-situ* ligand minimization. *In-silico* docking indicated indolizines is potential drugs for trpD and InhA targets with no toxicity. Hence, indolizines are promising inhibitors of InhA activity against multidrug-resistant TB strain [65].

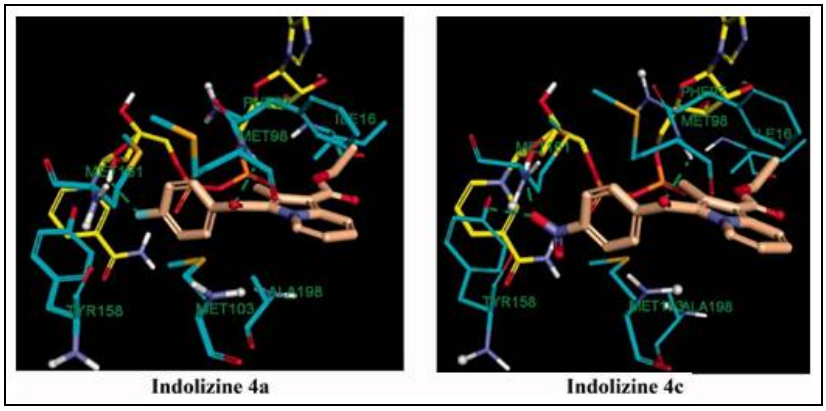

FIG. 5: PREDICTION OF INDOLIZINES–INHA BINDING DOMAIN INTERACTIONS. INHA – PDB 5G0S, CYAN: RECEPTOR, YELLOW: NAD (NICOTINE DIAMINE DINUCLEOTIDE), AND SOLMON: LIGAND, GREEN DOTS: HYDROGEN BONDS CONTACT

Twenty Benzimidazole derivatives' efficiency was initially evaluated for their anti-tuberculosis activity using the AutoDock Vina algorithm, further enhanced by Glide algorithm-mediated redocking. Molecular Docking of Benzimidazole ligands indicated hydrogen bond formation and strong binding affinity to the active site of PrpR, an *M. tuberculosis* protein in which amino acids residues like GLY189, LEU190, ARG308, VAL312, and LEU403 are anticipated binding of benzimidazole ligands. The results revealed the derivatives of benzimidazole are potent anti-tubercular molecules in contrast to the standard drug isoniazid [66].

A molecular docking study of 357 structural analogs of Azole drugs inhibits the CYP121 proteins of *M. tuberculosis* using CDOCKER (Discovery Studio, 2.0) and Ligscore 2, PLP1 scoring functions indicated 53 molecules better score than Azole drugs, and 5 of them ranked among the top 12 molecules. Since computational and gene-knockout studies indicated CYP121-based viability of *M. tuberculosis*, these proteins are potential targets for novel drug development. Azole drugs are fungal-based drugs that are extensively reported to inhibit CYP121 orthologs [67].

A molecular docking study evaluated the 1, 3, 4-thiadiazole derivatives revealing significant anti-TB activity with potent minimum inhibitory concentration (MIC) value to rationalize their biological outcome further. Docking was performed using Glide version 5.7 by selecting the complex of the crystal structure of InhA and inhibitor 1-cyclohexyl-N-(3,5-dichlorophenyl)-5-oxopyr-rolidine-3-carboxamide (PDB:2H7M) with 1.62Å resolution indicated −8.02 kcal/mol Glide score. The InhA inhibitor compound 11, 15 and 19 indicating potent MIC value against *M. tuberculosis* were used for docking against InhA indicating an excellent score of docking in the range of -7.12 to -7.83 kcal/mol in contrast to the less active compounds 6 and 17 docking score of −5.57 and −6.20 kcal/mol [68].

The potential leads such as ZINC000034268676, ZINC000000001392, ZINC000000157405 and ZINC000003958185 selected by virtual screening of natural compounds were characterized for binding interactions with OmpATb an outer membrane protein A of *M. tuberculosis*. The molecular dynamics simulation indicated the anticipation of PHE151, VAL146, SER145, ARG86, PHE142, ALA115, LEU114, LEU113, and LEU110, amino acids of OmpATb in the formation of stable lead-protein complex. These amino acid residues donate lower binding energy to molecules and OmpATb interactions. The poses of molecules are predicted by Induced Fit Docking using AutoDock Vina. ZINC000034268676 was found to be a potential lead in designing an inhibitor of OmpATb to enhance hydrophobic drug uptake that decreases the duration of TB treatment [69].

DISCUSSION: Adoption of docking techniques for rapid drug discovery is inevitable due to several threats to the healthcare industry, the emergence of drug resistance in medical pathogens, and increased viral diseases, as exemplified by recent coronavirus epidemics persisting all over the world. Moreover, in such an emergency, high throughput screening (HTS) of drug molecules may be fruitless in a limited time and expense. Even the outcome may not always result in isolating a novel bioactive molecule. It may be already isolated, a less potent molecule, or obtaining a novel, highly infrequent potent molecule.

A similar obstacle is also associated with screening existing drug databases for various biological activities. On the other hand, the numbers of newly FDA-approved drugs are drastically declining; for instance, merely 19 new molecular entities were approved in 2007 by USFDA, which is the least count since 1983 [70]. The astonishing present and future situation is that no new drug molecules are expected to enter the market. Only existing miracle drugs need to be modified to obtain a new lead, further complicating the problem as pharmaceutical industries are driven by innovative and miracle drugs [71].

Since, in the novel drug discovery process time and cost are two crucial factors, computer-aided drug design (CADD) like *In-silico* Molecular docking methods are increasingly becoming more popular, attractive, and unavoidable computational tools due to their applications in the rapid drug development process in limited budget. Moreover, most

software, programs, genomics, proteomics, and metabolomics required for molecular docking are freely available on various public websites. The advancement in Nuclear Magnetic Resonance Spectroscopy and 3D X-ray further enlarged the depository of PDB. For instance, at the end of 2008, in PDB total number of X-ray structure reported were 46,541, which was further grown to the astonishing count of 1,31,993 by the end of 2018 [72]. Henceforth, virtual screening has become a perfect computational method alternative to HTS in screening such a huge database in a few days, and its speed helps in identifying new leads [73].

One widely applied VS method is molecular docking exploited as a powerful tool in drug discovery and optimization. Over three decades, based on the scoring functions and search algorithms, several docking programs are developed that include AutoDock tools like AutoDock, AutoDock Vina, BDT, WinDock, AUDocker, VSDocker, DockoMatic, DOVIS, PyMOL AutoDock plugin, *etc.* [74]. Along with AutoDock programs, some of the extensively used docking routines are GOLD, FRED, and FlexX. Amidst docking programs, AutoDock Vina generates a 70% perfect pose as the method can bind beep inside the binding pocket of 5Å. However, FRED and FlexX predicta good pose of 45% and 65%, respectively and no significant pose is generated by FlexX. As far asthe average time needed for docking is concerned, the FlexX algorithm is more time taking and FRED is the fastest taking 1.4 seconds for single ligand docking followed by 1.66 and 2-3 seconds required by GOLD and AutoDock Vina [18].

The applications of molecular docking in drug discovery are witnessed by drugs in clinical use. Inhibition of HIV1 Integrase, a target for drug molecules used to treat AIDS was discovered with the help of AutoDock [75]. The virtual screening of 14,064 marine drugs is carried out to study the main protein (M^{pro}) of SARS-CoV-2 M^{pro} (Severe Acquired Respiratory Syndrome Coronavirus) using a hyphenated pharmacophore model. Further docking of 180 molecules using AutoDock Vina, molecular dynamics simulations, and AutoDock 4 resulted in 17 phloroglucinol oligomers isolated from brown alga *Sargassum spinuligerum* potentially inhibited the revealed SARS-CoV-2 M^{pro} with the highest docking score in comparison to the existing treatment of COVID-19 [76]. Molecular docking techniques also played a substantial role in anti-TB drug discovery. Drug design for anti-TB activity is mainly aimed at inhibition of various cellular targets of *M. tuberculosis* namely enzymes and cellular proteins having critical functions in cells and essential for bacterial survival example arabinosyltransferase C (cell wall synthesis), protein kinase A (cell shape and cell mechanics), and glutamine synthetase (inhibits host defense mechanism), *etc.*

The study of interactions of two drugs, Isoniazid and Ethambutol, with Arabinosyltransferase C using the molecular docking tool AutoDock 4 indicated successful inhibition of Arabinosyltransferase C [77]. Virtual screening of 3176 FDA drugs using molecular docking against the protein kinase A revealed vitamin B2-based compounds inhibition of protein kinase A. The study suggested that riboflavin and vitamin B2 substances may help treat TB by inhibiting the protein kinase A [78]. Similarly, the glutamine synthetase of *M. tuberculosis* is inhibited by trisubstituted Imidazoles, as revealed by docking studies [78]. Thus, the need CADD in the TB drug development process is huge and plays a major role in designing new leads to combat the TB pathogen, including multi-resistant ones.

CONCLUSION: The changing disease scenario, aggressive response of medical pathogens towards antibiotics like the emergence of antibiotic resistance, exhausting antibiotics, and lack of discovery of novel antibiotics are constantly threatening the health care system unless the approaches for innovative drug discovery are changed.

As discussed, the HTS technique is time-consuming and costly; to cope with the above situations, the CADD using computational techniques in the advanced drug development process is essential. Molecular docking offers several software programs for virtual screening for massive biological information for designing new leads or new molecule discoveries. Hence, molecular docking tools play a significant role in discovering new drugs at a limited time and expense.

ACKNOWLEDGEMENT: The Authors would like to thank the Principal, K. L. College of Pharmacy, for encouraging and supporting the manuscript's preparation.

CONFLICTS OF INTEREST: The Authors declared no conflict of interest.

REFERENCES:

1. Misra BB, Langefeld C, Olivier M and Cox LA: Integrated omics: tools, advances and future approaches. Journal of Molecular Endocrinology 2019; 62(1): 21-45.
2. Williams JJ, Drew JC, Galindo-Gonzalez S, Robic S, Dinsdale E, Morgan WR, Triplett EW, Burnette JM 3rd, Donovan SS, Fowlks ER, Goodman AL, Grandgenett NF, Goller CC, Hauser C, Jungck JR, Newman JD, Pearson WR, Ryder EF, Sierk M, Smith TM, Tosado-Acevedo R, Tapprich W, Tobin TC, Toro-Martínez A, Welch LR, Wilson MA, Ebenbach D, McWilliams M, Rosenwald AG and Pauley MA: Barriers to integration of bioinformatics into undergraduate life sciences education: A national study of US life sciences faculty uncover significant barriers to integrating bioinformatics into undergraduate instruction. PLoS One 2019; 14(11): e0224288.
3. Bayat A: Science, medicine, and the future: Bioinformatics. British Medical Journal Clinical Research 2002; 324: 1018–1022.
4. Mehmood MA, Sehar U and Ahmad N: Use of Bioinformatics Tools in Different Spheres of Life Sciences. Journal of Data Mining in Genomics & Proteomics 2014; 5:1-13.
5. Tutone M and Almerico AM: Computational Approaches: Drug Discovery and Design in Medicinal Chemistry and Bioinformatics. Molec Basel Switzerland 2021; 26: 7500.
6. Li XH, Chavali PL and Babu MM: Capturing dynamic protein interactions. Science New York, N.Y. 2018; 359: 1105–1106.
7. Pereira F and Aires-de-Sousa J: Computational Methodologies in the Exploration of Marine Natural Product Leads. Marine Drugs 2018; 16: 236.
8. World Health Organization (2020). Global tuberculosis report 2021. Retrieved from: https://www.who.int/publications/i/item/9789240013131. Accessed October 15, 2020.
9. World Health Organization (2019). Global tuberculosis report 2019.Retrieved from:https://www.who.int/publications/i/item/9789241565714. Accessed October 15, 2019.
10. Miotto P, Zhang Y, Cirillo DM and Yam WC: Drug resistance mechanisms and drug susceptibility testing for tuberculosis. Respirology 2018; 23(12): 1098-1113.
11. Ogwang MO, Imbuga M, Ngugi C, Mutharia L, Magoma G and Diero L: Distribution patterns of drug resistance Mycobacterium tuberculosis among HIV negative and positive tuberculosis patients in Western Kenya. BMC Infectious Diseases 2021; 21(1): 1175.
12. Rumende CM: Risk Factors for Multidrug-resistant Tuberculosis. Acta Medica Indonesiana 2018; 50(1): 1-2.
13. Prasad R, Singh A and Gupta N: Adverse drug reactions in tuberculosis and management. Indian Journal of Tuberculosis 2019; 66(4): 520-532.
14. Grüber G: Introduction: Novel insights into TB research and drug discovery. Progress in Biophysics and Molecular Biology 2020; 152: 2–5.
15. Lee AC, Harris JL, Khanna KK and Hong JH: A Comprehensive Review on Current Advances in Peptide Drug Development and Design. International Journal of Molecular Sciences 2019; 20(10): 2383.
16. Cicaloni V, Trezza A, Pettini F and Spiga O: Applications of *in-silico* Methods for Design and Development of Drugs Targeting Protein-Protein Interactions. Current Topics in Medicinal Chemistry 2019; 19(7): 534-554.
17. Arjmand B, Hamidpour SK, Alavi-Moghadam S, Yavari H, Shahbazbadr A, Tavirani MR, Gilany K and Larijani B: Molecular Docking as a Therapeutic Approach for Targeting Cancer Stem Cell Metabolic Processes. Frontiers in Pharmacology 2022; 13: 768556.
18. Azam SS and Abbasi SW: Molecular docking studies for the identification of novel melatoninergic inhibitors for acetylserotonin-O-methyltransferase using different docking routines. Theoretical Biology & Medical Modelling 2013; 10: 63.
19. Saikia S and Bordoloi M: Molecular Docking: Challenges, Advances and its Use in Drug Discovery Perspective. Current Drug Targets 2019; 20(5): 501-521.
20. Yadava U: Search algorithms and scoring methods in protein-ligand docking. Endocrinology Metabolism International Journal 2018; 6(6): 359–367.
21. Fischer E: Influence of configuration on the effect of enzymes. Berichte der Deutschen Chemischen Gesellschaft B 1894; 27: 3189–3232.
22. Koshland DE: Application of a Theory of Enzyme Specificity to Protein Synthesis. Proceedings of the National Academy of Sciences of the United States of America 1958; 44: 98–104.
23. Chen G, Seukep AJ and Guo M: Recent Advances in Molecular Docking for the Research and Discovery of Potential Marine Drugs. Marine Drugs 2020; 18: 545.
24. Bitencourt-Ferreira G, Veit-Acosta M and de Azevedo WF: Van der Waals Potential in Protein Complexes. Methods Molecular Biology 2019; 2053: 79-91.
25. Hermosilla P, Estrada J, Guallar V, Ropinski T, Vinacua A and Vazquez PP: Physics-Based Visual Characterization of Molecular Interaction Forces. IEEE Transactions on Visualization and Computer Graphics 2017; 23: 731-740.
26. Scarpino A, Ferenczy GG and Keserű GM: Covalent Docking in Drug Discovery: Scope and Limitations. Current Pharmaceutical Design 2020; 26(44): 5684-5699.
27. Liu Z, Liu Y, Zeng G, Shao B, Chen M, Li Z, Jiang Y, Liu Y, Zhang Y and Zhong H: Application of molecular docking for the degradation of organic pollutants in the environmental remediation: A review. Chemosphere 2018; 203: 139–150.
28. Rarey M, Kramer B and Lengauer T: Multiple automatic base Selection: protein-ligand docking based on incremental construction without manual intervention. Journal of Computer-aided Molecular Design 1997; 11: 369–384.
29. Schulz-Gasch T and Stahl M: Binding site characteristics in structure-based virtual screening: evaluation of current docking tools. Journal of Molecular Modelling 2003; 9: 47–57.
30. Gioia D, Bertazzo M, Recanatini M, Masetti M and Cavalli A: Dynamic Docking: A Paradigm Shift in Computational Drug Discovery. Molecules (Basel, Switzerland) 2017; 22: 2029.
31. Feng Z, Verdiguel N, Di Costanzo L, Goodsell DS, Westbrook JD, Burley SK and Zardecki C: Impact of the Protein Data Bank Across Scientific Disciplines. Data Science Journal 2020; 19(1): 25.

32. De Vita S, Lauro G, Ruggiero D, Terracciano S, Riccio R and Bifulco G: Protein Preparation Automatic Protocol for High-Throughput Inverse Virtual Screening: Accelerating the Target Identification by Computational Methods. Journal of Chemical Information Modeling 2019; 59(11): 4678-4690.
33. Chatterjee A, Roy UK and Halder D: Protein Active Site Structure Prediction Strategy and Algorithm. International Journal of Current Engineering and Technology 2017; 7(3): 1092-1096.
34. Lipinski CA, Lombardo F, Dominy BW and Feeney PJ: Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced drug delivery reviews 2001; 46(1-3): 3–26.
35. Torres P, Sodero A, Jofily P and Silva-Jr FP: Key Topics in Molecular Docking for Drug Design. International Journal of Molecular Sciences 2019; 20: 4574.
36. Snyder HD and Kucukkal TG: Computational Chemistry Activities with Avogadro and ORCA. Journal of Chemical Education 2021; 98(4): 1335–1341.
37. Pagadala NS, Syed K and Tuszynski J: Software for molecular docking: a review. Biophysical reviews 2017; 9(2): 91–102.
38. Li J, Song Y, Li F, Zhang H and Liu W: FWAVina: A novel optimization algorithm for protein-ligand docking based on the fireworks algorithm. Computational Biology Chemistry 2020; 88: 107363.
39. Novič M, Tibaut T, Anderluh M, Borišek J and Tomašič T: The Comparison of Docking Search Algorithms and Scoring Functions: An Overview and Case Studies. In I. Management Association (Ed.), Pharmaceutical Sciences: Breakthroughs in Research and Practice 2017; 820-849. IGI Global.
40. Raval K and Ganatra T: Basics, types and applications of molecular docking: A review. International Journal of Comprehensive Advanced Pharmacol 2022; 7(1): 12-16.
41. Li J, Liu G, Zhen Z, Shen Z, Li S and Li H: Molecular Docking for Ligand-Receptor Binding Process Based on Heterogeneous Computing. Scientific Programming 2022; 2022: 9197606.
42. Li J, Fu A and Zhang L. An Overview of Scoring Functions Used for Protein-Ligand Interactions in Molecular Docking. Interdisciplinary Sciences 2019; 11(2): 320-328.
43. Makhouri FR and Ghasemi JB: Combating Diseases with Computational Strategies Used for Drug Design and Discovery. Current Topics in Medicinal Chemistry 2018; 18: 2743–2773.
44. Barbosa DA and Piccoli FP: Comparing the force due to the Lennard-Jones potential and the Coulomb force in the SPH Method. Journal of ocean engineering and science 2018; 3(4): 310-315.
45. Jespers W, Åqvist J and Gutiérrez-de-Terán H: Free Energy Calculations for Protein-Ligand Binding Prediction. Methods in Molecular Biology 2021; 2266: 203-226.
46. Fratev F and Sirimulla S: An Improved Free Energy Perturbation FEP+ Sampling Protocol for Flexible Ligand-Binding Domains. Scientific Reports 2019; 9: 16829.
47. Hao D, He X, Ji B, Zhang S and Wang J: How Well Does the Extended Linear Interaction Energy Method Perform in Accurate Binding Free Energy Calculations. Journal of Chemical Information and Modeling 2020; 60(12): 6624-6633.
48. Briggs JM, Marrone TJ and McCammon JA: Computational science new horizons and relevance to pharmaceutical design. Trends in Cardiovascular Medicine 1996; 6: 198–203.
49. Madhavilatha KN and Mohan Babu GR: Systematic approach for enrichment of docking outcome using consensus scoring functions. Journal of Physics Conference Series 2019; 1228: 012019.
50. Desta IT, Porter KA, Xia B, Kozakov D and Vajda S: Performance and Its Limits in Rigid Body Protein-Protein Docking. Structure 2020; 28(9): 1071-1081.e3.
51. Ewing TJ, Makino S, Skillman AG and Kuntz ID: DOCK 4.0: search strategies for automated molecular docking of flexible molecule databases. Journal of Computer-aided Molecular Design 2001; 15: 411–428.
52. Hayashi T, Matsuzaki Y, Yanagisawa K, Ohue M and Akiyama Y: MEGADOCK-Web: an integrated database of high-throughput structure-based protein-protein interaction predictions. BMC Bioinformatics 2018; 19(4): 62.
53. Butt SS, Badshah Y, Shabbir M and Rafiq M: Molecular Docking Using Chimera and Autodock Vina Software for Nonbioinformaticians. JMIR Bioinformatics Biotechnology 2020; 1(1): 14232.
54. Bitencourt-Ferreira G, Pintro VO and de Azevedo WF: Docking with AutoDock4. In: de Azevedo, W. (eds) Docking Screens for Drug Discovery. Methods in Molecular Biology 2019; 2053: 125-148.
55. Feng LX, Jing CJ, Tang KL, Tao L, Cao ZW, Wu WY, Guan SH, Jiang BH, Yang M, Liu X and Guo DA: Clarifying the signal network of salvianolic acid B using proteomic assay and bioinformatic analysis. Proteomics 2011; 11: 1473–1485.
56. Pantsar T and Poso A: Binding Affinity via Docking: Fact and Fiction. Molecules 2018; 23(8): 1899.
57. Verdonk ML, Cole JC, Hartshorn MJ, Murray CW and Taylor RD: Improved protein-ligand docking using GOLD. Proteins 2003; 52: 609–623.
58. Issa NT, Badiavas EV and Schürer S: Research Techniques Made Simple: Molecular Docking in Dermatology - A Foray into *In-silico* Drug Discovery. Journal of Investigative Dermatology 2019; 139(12): 2400-2408.
59. Gudipati S, Muttineni R, Mankad AU, Pandya HA and Jasrai YT: Molecular docking based screening of Noggin inhibitors. Bioinformation 2018; 14(1): 15-20.
60. Venkatachalam CM, Jiang X, Oldfield T and Waldman M: Ligand Fit: a novel method for the shape-directed rapid docking of ligands to protein active sites. Journal of Molecular Graphics & Modelling 2003; 21: 289–307.
61. Bartuzi D, Kaczor AA, Targowska-Duda KM and Matosiuk D: Recent Advances and Applications of Molecular Docking to G Protein-Coupled Receptors. Molecules (Basel, Switzerland) 2017; 22: 340.
62. Tessaro F and Scapozza L: How 'Protein-Docking' Translates into the New Emerging Field of Docking Small Molecules to Nucleic Acids. Molecules 2020; 25(12): 2749.
63. Eberhardt J, Santos-Martins D, Tillack AF and Forli S: AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings. Journal of Chemical Information and Modeling 2021; 61(8): 3891-3898.
64. Khan T, Lawrence AJ, Azad I, Raza Sand Khan AR: Molecular Docking Simulation with Special Reference to Flexible Docking Approach. JSM Chemistry 2018; 6(1): 1053.
65. Venugopala KN, Chandrashekharappa S, Deb PK, Tratrat C, Pillay M, Chopra D, Al-Shar'i NA, Hourani W, Dahabiyeh LA, Borah P, Nagdeve RD, NayakSK, Padmashali B, Morsy MA, Aldhubiab BE, Attimarad M,

Nair AB, Sreeharsha N, Haroun M, Shashikanth S and Mailavaram R. Anti-tubercular activity and molecular docking studies of indolizine derivatives targeting mycobacterial InhA enzyme. Journal of Enzyme Inhibition and Medicinal Chemistry 2021; 36: 1472–1487.

66. Rajasekhar S, Karuppasamy R and Chanda K: Exploration of potential inhibitors for tuberculosis *via* structure-based drug design, molecular docking, and molecular dynamics simulation studies. Journal of Computational Chemistry 2021; 42: 1736–1749.
67. Sundaramurthi JC, Kumar S, Silambuchelvi K and Hanna LE: Molecular docking of azole drugs and their analogs on CYP121 of Mycobacterium tuberculosis. Bioinformation 2011; 7: 130–133.
68. Tatar E, Karakuş S, Küçükgüzel Ş G, Öktem Okullu S, Ünübol N, Kocagöz T, De Clercq E, Andrei G, Snoeck R, Pannecouque C, Kalaycı S, Şahin F, Sriram D, Yogeeswari P and Küçükgüzel İ: Design, Synthesis and Molecular Docking Studies of a Conjugated Thiadiazole-Thiourea Scaffold as Antituberculosis Agents. Biological & Pharmaceutical Bulletin 2016; 39: 502–515.
69. Kwofie SK, Adobor C, Quansah E, Bentil J, Ampadu M, Miller WA and Wilson MD: Molecular docking and dynamics simulations studies of OmpATb identifies four potential novel natural product-derived anti-Mycobacterium tuberculosis compounds. Computers in Biology and Medicine 2020; 122: 103811.
70. Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR and Schacht AL: How to improve R & D productivity: the pharmaceutical industry's grand challenge. Nature reviews. Drug Discovery 2010; 9: 203–214.
71. Karamehic J, Ridic O, Ridic G, Jukic T, Coric J, Subasic D, Panjeta M, Saban A, Zunic L and Masic I: Financial aspects and the future of the pharmaceutical industry in the United States of america. Materia Socio-medica 2013; 25: 286–290.
72. Protein data bank: PDB Statistics: Growth of Structures from X-ray Crystallography Experiments Released per Year. Retrieve from: https://www.rcsb.org/stats/growth/growth-xray. Accessed February 6, 2022.
73. Alvarez JC: High-throughput docking as a source of novel drug leads. Current Opinion in Chemical Biology 2004; 8: 365–370.
74. Valdés-Tresanco MS, Valdés-Tresanco ME, Valiente PA and Moreno E: AMDock: a versatile graphical tool for assisting molecular docking with Autodock Vina and Autodock4. Biology Direct 2020; 15: 12.
75. Schames JR, Henchman RH, Siegel JS, Sotriffer CA, Ni H and McCammon JA: Discovery of a novel binding trench in HIV integrase. Journal of Medicinal Chemistry 2004; 47: 1879–1881.
76. Gentile D, Patamia V, Scala A, Sciortino MT, Piperno A and Rescifina A: Putative Inhibitors of SARS-CoV-2 Main Protease from A Library of Marine Natural Products: A Virtual Screening and Molecular Modeling Study. Marine Drugs 2020; 18: 225.
77. Das N, Jena PK and Pradhan SK: Arabinosyltransferase C enzyme of Mycobacterium tuberculosis, a potential drug target: An insight from molecular docking study. Heliyon 2020; 6: 02693.
78. Sundar S, Thangamani L, Manivel G, Kumar P and Piramanayagam S: Molecular docking, molecular dynamics and MM/PBSA studies of FDA approved drugs for protein kinase a of Mycobacterium tuberculosis; application insights of drug repurposeing. Informatics in Medicine Unlocked 2016; 16: 100210.
79. Gising J, Nilsson MT, Odell LR, Yahiaoui S, Lindh M, Iyer H, Sinha AM, Srinivasa BR, Larhed M, Mowbray SL and Karlén A: Trisubstituted imidazoles as Mycobacterium tuberculosis glutamine synthetase inhibitors. Journal of Medicinal Chemistry 2012; 55: 2894–2898.

How to cite this article:
Asra F, Dumala N, Ajra F, Mallika S and Vadivel K: Molecular docking as an ideal tool in pharmaceutical drug development of anti-tuberculosis molecules. Int J Pharm Sci & Res 2023; 14(4): 1534-46. doi: 10.13040/IJPSR.0975-8232.14(4).1534-46.