Review Article

A Review: In – Silico Approaches in Predictive Toxicology

Sachin M. Mendhi,*[1] Sachin M. More,*[2] Manoj S. Ghoti[3], Mandar A. Thool[4], Rinkesh M. Tekade[5].
Assistant Professor, Department of Pharmacology, Dadasaheb Balpande College of Pharmacy, Besa, Nagpur, Maharashtra, India[1,2].
Student, Dadasaheb Balpande College of Pharmacy, Besa, Nagpur, Maharashtra, India.[3,4,5]
***Corresponding author's E-mail:** sachin24mendhi@gmail.com

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ABSTRACT

This article deals with the in – silico techniques for predicting the toxicity of chemical compounds. Toxicology is the branch of biology that deals with the study of adverse effect of chemical substances on the living organisms and the practice of treating and preventing such adverse effects. Predicting toxicity of a new drug to be produced is the first aim of preclinical trials. It is achieved by in-silico methods. There are several in - silico technique softwares which are used for the prediction of ADME and hence toxicity of drugs. In – silico methods involves the use of various softwares to calculate and then predict the toxicity of a compound by first determining its structural and pharmacokinetic and pharmacodynamic properties and then it correlates this information with already existing drugs and molecules and thus gives us conclusion. The article focuses on QSAR and its techniques, HQSAR, several other methods like structural alerts and rule-based models, chemical category and read across model, dose and time response model, virtual ligand screening, docking, 3D pharmacophore mapping, simulation approaches, PKPD models and several other approaches like bioinformatics. After reviewing and studying various in silico techniques the conclusion comes out to be that, in-silico methods of predictive toxicology are more better than in-vitro and in-vivo methods since they are much more safe (as animals are not harmed), economic, fast and accurate w.r.to, results/output in predicting toxicity of compounds by computational methods and hence are widely used in the production of new drug for accessing its toxicity.

Keywords: In silico, predictive toxicology, QSAR, docking and bioinformatics.

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INTRODUCTION

Predicting toxicity of a new drug to be produced is the first aim of preclinical trials. It is achieved by in-vivo, in-vitro and in-silico methods. This article deals with the in-silico approaches commonly used in drug development.

Toxicology is the branch of biology that deals with the study of adverse effect of chemical substances on the living organisms and the practice of treating and preventing such adverse effects. Factors which influence toxicity include dose, route, species, age, gender and individual characteristics.

Importance of toxicity prediction

1. To identify potential hazardous compounds that could draw into manufacturing.
2. Essential to save cost of preclinical trials of a toxic drug which will be rejected further.
3. To produce a safe and effective drug for the treatment of health conditions.

Advantages of in - silico toxicity prediction[1]

1. Eliminates potential toxic compounds.
2. Animals are not sacrificed.
3. We can introduce safe drug in the market.
4. It saves cost of further trials of toxic compounds.
5. Fast as compared to in-vivo and in-vitro practices.

Disadvantages of toxicity prediction[1]

1. Many times, costly.
2. Many compounds get rejected out of thousands and only few reach to next stage of trials.
3. As very few out of thousands reach to next stage, there is always a fear of great economic loss towards the end.

Toxicology as a science and regulatory approvals, have the goal of ensuring the safety of humans, animals and the environment. Evaluation of risks of all chemical categories (drug) to the body is still mainly based animal experimentation. Developments in knowledge of cellular pathways, genetics and modeling have resulted in better understanding of the molecular mechanisms of xenobiotic action and toxicity. Integrated risk assessment approach

includes evaluation of chemical functionalities representing structural alerts for toxic actions[1].

In – vivo methods involves experiments or testing within living organism, animal models and human clinical trials. In - vitro methods are performed with microorganisms and cells and are done in test tubes, flasks, petri dishes, etc.

In-silico methods for drug development involves the use of various computer softwares. The methods are particularly oriented towards the identification of the molecular structure of a new compound and then its alteration so as to achieve the highest efficacy and min. toxicity. This method involves various software techniques like QSAR, Molecular Docking, Homology Modeling, etc. By the use of these techniques molecular structure of compound/lead & its receptor occupancy can be determined, thus it enables us to confirm the target which further helps us to develop new DDS. Once the target is identified by these techniques drug can be further developed to reduce its toxicity and increase its efficacy[1].

Comparison of methods to study absorption:-

Table 1: Comparison of methods to study absorption [2]

In-vitro	In-vivo	In-silico
Absorption:- 1. Diffusion cells 2. Everted sac 3. Everted ring.	Absorption:- 1. Doluisio method 2. Single pass perfusion.	Absorption:- 1. PAMPA (Parallel Artificial Membrane Permeability Assay).

Quantitative Structure Activity Relationship (QSAR)

Quantitative structure activity relationship (QSAR) models are mathematical models which are used to predict the structure of a particular compound and its relationship with biological activity with the aid of structure. QSAR correlates molecular structure of a lead with its pharmacokinetics and pharmacodynamic properties. QSAR also involves the use of molecular discriptors.[3, 4]

Steps of QSAR include, 1. Selection of Data set and extraction of structural descriptors 2. Variable selection i.e., selection of most relevant structures 3. Model construction and 4. Validation and evaluation.[3, 4]

Types of QSAR,[4]

1. Fragment based :- Partition coefficient is used for predictions.
2. 1D – QSAR :- Molecular properties are encoded numerically and are correlated to biological activity.
3. 2D - QSAR :- Correlation of various 2D properties like physico- chemical properties with the biological activity. 2D structure of lead.
4. 3D – QSAR :- Uses 3D structure of a molecule for predctions.
5. 4D – QSAR :- Determination on ligand receptor interaction with 3D structure of lead. Averaging of the information obtained in 3D.
6. 5D – QSAR :- Represents several induced fit models in 4D QSAR.

Techniques used in 3D QSAR

CoMFA

Comparative molecular field analysis gives a correlation between biological activity and a set of molecules and their 3D shape, electrostatic and hydrogen bonding characteristics. Molecules are placed in cubic grid and the interaction energy between molecule and probe is calculated for each grid point.[4]

Process

Set of molecules interacting with the same receptor is selected. Several low energy confirmations are selected. Orientation of molecules on the receptor and binding affinity are calculated. Then grid distance is calculated and molecular properties like bonds, lipophilicity and binding energy is determined / calculated. Finally, PLA (Partial least square analysis) is done. Results of PLA are like regression equations. Data obtained is presented in the form of contour maps, which shows electron releasing and withdrawing substituents favoured positions for binding.[4]

CoMSIA

In Comparative Molecular Similarity Indices Analysis molecular similarity indices calculated from modified SEAL similarity field are used to determine steric, electrostatic, hydrophobic and hydrogen bonding properties. Similarity of molecules(atoms) are compared with probe atom at intersections of surrounding grid. Gaussian type functions are used.[5, 6]

Parameters used in QSAR,

1. Lipophilic parameters:- Partition coefficient and π-substitution constant.
2. Polarizability parameters:- Molar refractivity and parachor.
3. Electronic parameters:- Hammet constant and dipole moment.
4. Steric parameters:- Taft's constant.
6. Miscellaneous parameters:- Molecular weight and geometric parameters.

Partition coefficient

Conc. of drug in the lipid phase to aq. Phase.

Log 1/c = k1 log p + k2, where k1 and k2 are constant, log Po represent optimum Po/w for activity.

Taft steric parameters

By measuring rate of hydrolysis of ester. Determined the influence of the steric effect on the structure and shape of lead/drug. Nonbonding interactions that influence the shape and reactivity of ions and molecules are known as steric effect.

$Es = \log (Kx / K_H)_A$

Where Kx and K_H represent the rate of hydrolysis of substituted methyl acetate and unsubstituted methyl acetate.

Hammet electronic parameters

Hammet gives the electronic properties of a drug in relation to its activity. Describes the electronic effect of substituent at meta and para position on the aromatic ring. The Hammett constant(σ). Hammett considers both resonance and inductive effects.

$$\sigma_X = \log K_X - \log K_H$$

Electron withdrawing groups are characterized by positive σ values while electron donating substituent have negative σ value.

Hansch Analysis

The biological activity of a compound is based on its ability to reach the site of action and then to bind to the target receptor. Binding of the drug to the receptor depend on its shape, electron distribution and polarity of the groups involved in binding. Biological activity can be related to these factors by,

Log 1/c = k1 (partition parameters) + k2 (electronic parameters) + k3 (steric parameters) + k4

where, C = min. conc. for response.

K = constant.

$$\text{Log } (1/C) = k1P - k2P2 + k3\sigma + k4Es + k5$$

Other parameters can be substituted for p, σ and Es.

Free Wilson Analysis

Introduction of a particular substituent at a particular molecular position leads to similar biological activity, i.e., biological activity of parent is compared with lead.[3-6]

There are several models which are used to predict the drugs toxicity in QSAR[3-6].

Models

1. Data Mining:- It is the process of finding and extracting useful information from data sets.
2. Matched molecular pair analysis:- It compares properties of two molecules which differ only by one substituent.

Molecular descriptors

Molecular descriptors used in QSAR are classified according to dimensions i.e., 1D,2D and 3D. 1D descriptors stores the molecular information numerically i.e., it encodes molecular properties such as molecular weight, molar refractivity, octanol/water Po/w etc. numerically. Thus, we are able to know the molecule size and shape and its lipophilicity. Construction of a molecular structure from its topological characteristics is known as 2D QSAR. It tells us physicochemical properties. [3-6]

Hologram quantitative structure activity relationship HQSAR

In this technique there is no need for the 3D structure of the molecule. It is 2D fragment based QSAR. In this technique molecule breaks into molecular fingerprint fragments (linear or branched). Fragment size is usually 4-7 atoms. Then these molecular fingerprints are cut into strings at a fixed interval as specified by a hologram length (HL) parameter and then again sliced into fixed length. It depends on three main parameters, HL, fragment size and fragment distinction[atoms(A), bonds(B), connections(C), chirality(Ch) and donar and acceptor(DA)]. After this process fragment distinction analysis (Partial Least Square) is done. PLA finds a linear relationship between predicted variables and observed variables. Different combinations of these parameters are considered. After PLS several QSAR models are generated for each different fragment. The model generated is validated using Leave-One-Out (LOO) cross validation. LOO is used for the knowing that how the outputs of the statistical analysis will be generalized. It is mainly used for the prediction where we want to know that how accurately the predictive model will perform actually.[6]

Simulation Approaches

Simulation is the representation of the real process to explain that process with the help of computer animations.

Monte Carlo simulation

Mathematical Used to calculate thermodynamic, structural and statistical properties. Used to predict the probability of different outcomes when interventional variable is present. It assumes that each activity is independent.[6]

Molecular dynamic (MD) simulation

Computer simulation method for the analysis of movements of atoms and molecules. Newton's equation of motion for a system of interacting particles is used.[6]

Structural alerts and Rule - based model

Structural alerts (toxicophores or toxic fragment) are chemical structures that are associated to toxicity.

There are two main type of rule-based models that we will consider human-based rules (HBRs) and induction-based rules (IBRs). Human - based rules are obtained from human knowledge of experts and from literature and IBRs are derived computationally. HBRs are more accurate but are limited to human knowledge which may remain incomplete. Induction – based rules are implemented using probabilities to determine that if structural alerts corresponds to the toxic or non - toxic class. There are hybrid-based rule systems that contain IBRs and HBRs.[7, 8]

It is easy to interpret and implement structural alerts, they are useful in drug design to determine how drugs should be altered to reduce their toxicity. Structural alerts have a number of limitation, structural alerts use only binary features (e.g. chemical structure are either present or absent) and only qualitative endpoint (e.g. carcinogenic or non- carcinogenic). If a chemical does not include structural alerts or does not match any toxicity rules this does not indicate non – toxicity. In developing such model, it is necessary to ensure that the list of structural alerts is present and that they are refined when more experimental data become available. If they are too narrow, they can be applied only to a small group of chemicals and this may increase false negative (i.e. toxic chemical predicted as non - toxic) result.[7, 8]

Chemical - Category versus Read - Across

Chemicals in certain category are also known as source chemicals. The OECD guidance on grouping of chemicals. Several method for grouping, such as chemical identify and composition, physicochemical properties and ADME properties, Mechanism of action (MAO) and chemical or biological interaction. Structural similarity is described in the OECD guidelines and it can be used if impurities or other constituents in the chemical composition would not change toxicity.[7, 8]

Read-Across is a method of predicting unknown toxicity of a chemical using similar chemical with known toxicity from the same chemical category. Read-Across can be qualitative if the toxicity endpoint is qualitative and quantitative if the read-across is quantitative.[7, 8]

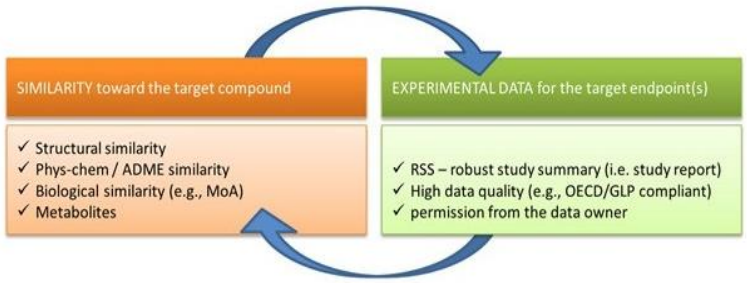

Figure 1: Requisite for analogue(s) suitable for read-across

Read - across identifying similar chemical can be done in two steps, representing chemicals as feature vectors of chemical properties and then calculating similarity of chemicals. First step is implemented using binary or holographic fingerprint methods. A binary fingerprint is features vector of binary bits which represents presence or absence of specific property (e.g. presence of methyl group). A holographic fingerprint uses frequency of properties such as (e.g. number of methyl groups). Continuous properties (chemical properties e.g. melting point) can also be used. Number and choice of similarity measures. An example of hierarchal categories has provided statistical similarity of two chemicals and can be calculated using different types of distance such as Hamming, Euclidean, cosine, Tanimoto. Different properties of Read-Across models explain with figure no.2.[7, 8]

Figure 2: Different properties of Read – Across models [8]

There are several advantages of read – Cross. It is transparent, easy to interpret and implement and it allows for a wider range of types of descriptors and similarity measures to be use to express similarity between chemical slimitation of read-across model. Statistical similarity measures does not provide insights of toxicity, read-across uses small datasets as compared to other techniques such as QSAR because there are usually only few analogues for a given chemical. Read-across was applied to predict carcinogenicity, hepatotoxicity, aquatic toxicity, reproductive toxicity, skin sensitization and environmental toxicity.[7, 8]

Dose - Response and Time - Response models

Dose - response (or time- response) models are relationship between does (or time) and the incidence of a defined biological effect (e.g. toxicity or mortality). A dose is, quantity of a substance administered to, taken up, or absorbed by an organism, organ or tissue and can be measured with in vivo or vitro experiments. Time dose models described the relationship between time and dose for a constant response. Figure 3 shows different types of dose times - response models. These models described relationship between response versus dose or time. Dose and time response graphs can be produced by regression to best fit the data.[8]

First model correlates concentration and time with response (toxic effect), which is Haber's law (law of toxicity). $C \times t = K$

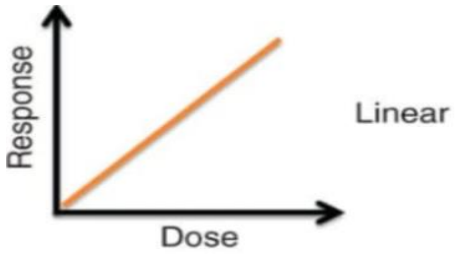

Figure 3: Type of dose response relationship[8]

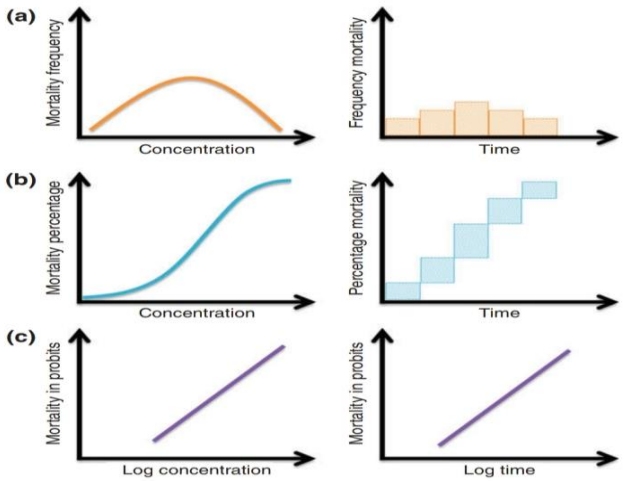

Figure 4: Bliss method,[8] A. plot mortality frequency verses dose or time B. Convert frequency to percentage (percentage of decreased subjects). C. Transform percentage to probits and transform dose or time to logarithms[8].

The law assume that any combination of concentration and time that has the same effect. One of the frequently measured responses is mortality (the number of decreased individuals). The Bliss method or (probir model) figure 4. transforms time - mortality and dose - mortality relationship into linear relationship.[8]

This model takes into consideration the variation of an individual's susceptibility to toxic agents, e.g. a certain dose (or time exposure) can cause the mortality of some individual but not other. [8]

There are many inherited difference between dose - mortality and time - mortality. Time mortality curves are determined for same individual whose susceptibility is measured at specific time intervals. The percentage of mortality of a given intervals can not be less than that of the preceding intervals and the susceptibility of individual, dose mortality curves are based on different individual for each dose . Therefore, susceptibility of individual to successive doses is unrelated especially if there are individuals who have high toxicity resistance.[8]

There are many advantages of this model. It is easy to interpret, implement and interpolation of effects between different doses of the same chemical within the range of experimental data is also easy.[8]

There are many limitation, the three models cannot extrapolate to other chemicals. Additionally, time - response models cannot extrapolate to other doses of the same chemical. Biological process, ADME, target tissue, toxicokinetics, toxicodynamics, detoxification, damage or repair or chemical properties are not considered in three methods (models). Several databases include dose - response data such as CEBS, pubchem, and ToxRefDB. These models were used, for example, for modelling rectal cancer, mutagenicity and development toxicity .[8]

Virtual Ligand Screening

In this technique, scores are given to molecule based on its structure and then we assign rank to it according to its affinity for target (receptor). Higher rank is given for higher affinity.

It is a knowledge-based approach, for which known molecular structure is necessary. This is known as Ligand based Virtual Screening (Ligand based affinity profiling methods).Target based Virtual Screening is used for the determination of the target(Target based affinity profiling methods). All these methods are based on the principle of central similarity, which states that, “similar structural molecules should have similar properties”. It also involves pharmacophore.[9]

For target-based screening methods, structure of target must be known which is determined either experimentally or by homology modeling. These target-based methods tells us the conformation and specific orientation of the

ligand on the target binding site known as docking and it also tells binding affinity known as scoring.[9]

Docking

It is a technique by which we can superimpose 3D structure of a drug on its target site. It also predict strength of binding, energy of complex and calculate binding affinity between two molecules using scoring function. Molecular docking predicts the structure of the complex formed between two molecules. It has two parts i.e., search algorithm and scoring functions.[10]

Search algorithm

It creates optimum number of configurations of binding modes. Ex. Molecular dynamics, Genetic algorithms, Fragment based methods, Distance geometry methods, systematic searches, etc.[10]

Scoring functions

Mathematical methods which predict the strength of non - covalent interactions known as binding affinity and strength between two molecules after they have been docked.[10]

Binding energy, ΔG bind = ΔG vdw + ΔG h bond + ΔG elect + ΔG conform + ΔG tor + ΔG sol

Figure 5: Docking Process

Types of docking

Lock and key / Rigid dock

Protein and ligand are considered as rigid. Internal geometry of the ligand and the receptor are fixed and docking is done.[10]

Induced fit / Flexible dock

Protein and ligand are flexible. Binding affinity of the molecule for each position with the receptor is calculated and thus the most efficient position is selected.[10]

Semi-flexible dock

Protein regid and ligand is considered as flexible.[10]

Steps

1. Preparation of protein structure (receptor) from PDB.
2. Active site prediction.
3. Preparation (retrieve) of ligand from database such as ZINC, Pub Chem or drawn by Chem sketch tool.
4. Docking of ligand and receptor.[10, 11]

Softwares used for docking are, GOLD, AUTO DOCK, SANJEEVINI, FTDOCK, I Gem dock and DISCOVERY STUDIO, etc.[10, 11]

Docking softwares and their description

Table 2: Docking softwares and their description.[10]

Docking softwares	Description
Gold	Uses genetic algorithm and gold score.
DOCK	Uses shape fitting (Sphere sets) and Chem Score.
FRED	Uses shape fitting (Gaussian) and Gaussian shape score.
AUTO DOCK	It uses several approaches like automated docking of ligand to macromolecule by Lamarckian genetic algorithm and empirical free energy scoring function.

3D pharmacophore mapping

Is the specific 3D arrangement of the functional groups a molecule which is required for proper binding. It is the combination of steric, electrostatic and hydrophobic properties which are essential for optimum supramolecular interactions with a receptor to promote or inhibit biological response. Steps of identifying pharmacophore are; input, conformational search, feature extraction, structural representation, pattern identification and scoring. Used to determine essential properties which are required for the binding of the molecule with the receptor.[12]

Model development

1. Selecting a training set of ligands:- structurally diverse set of molecules(Ligands; active and inactive) are choosen for development.
2. Conformational analysis:- Study of different energy levels of a moleculeassociated with different conformations of molecule. Used for determining most suitable 3D conformation.
3. Molecular superimposition:- may be done with the help of docking.

4. Abstraction:- Abstract representation of a molecule.
5. Validation:- Validate the lead by hypothesis testing and statistical analysis.

Pharmacophore is used to determine the features of one or more molecules with same biological activity as that of the known drug.[12]

Pharmacokinetic and pharmacodynamic models

Pharmacokinetics models relate chemical concentration in tissues to time, estimate the amount of chemical in different parts of the body, and quantify ADME processes. Used to correlate chemical concentration in tissues versus time of toxic/undesired effect. Pharmacokinetic models can be compartmental and non-compartmental. Compartmental models consist of one or more compartments, and each compartment is usually represented by different equation.[13]

One-compartment models explain and represent whole body as a single compartment, assume rapid equilibrium of chemical concentration within the body after administration. Concentration "C" at a given time t is calculated by,

$$C(t) = C0 \times e^{-kt}$$

Where, C0 = initial concentration and

K = elimination constant.

Plot of log concentration versus time results in a straight line of slope (-kt). Concentration in some organs of body attains equilibrium faster than in others.

Two -compartment models consist of two compartments i.e., central compartment (for rapidly- perfused tissue e.g., liver or kidney) and peripheral compartment (for slowly perfused tissues e.g., muscle or skin). After solving the coupled equation, sum of two exponential terms of time (interpreted as distribution phase with initial concentration Ca and slope -a and elimination phase with initial concentration Cb and slope –b) is the concentration.[13]

$$C(t) Þ = Ca \times e^{-at} + Cb \times e^{-bt}$$

Physiological based pharmacokinetics (PBPK) model include, in addition to concentration and time, physiological descriptors of tissue and ADME process such as volume, blood flow, chemical binding, partitioning, metabolism or excretions. A general PBPK model to calculate plasma concentrations (cp) uses a feature vectors of pk parameters (θPK), time (t) and dose (x) as follows.[13]

$$CP = f(\theta PK, \times, t)$$

Where f = function which models relationship because equation structure and the physiological parameters are tissue specific.

Pharmacodynamic (PD) models relate biological response to the concentration of chemical in tissue. PD models can be linear or nonlinear. Linear models does not consider the upper limit of responses and assumes that responses always increase when concentration increases. A general PBPD model gives response (R) using a feature vector of PD parameters (θPD) plasma concentrations (CP) , which is calculated using the PBPK models or biophase concentration (Ce) and chemical-independent system parameters (z) can be represented as,

$$R = f(\theta PD, cp \text{ or } ce, z)$$

where, f = function that models relationship.

Pharmacodynamic models can be combined with pharmacokinetic models and the resulting model is called biologically based dose-response model (BBDR). It can be used to correlate dose with response. Biologically based dose-response models are more powerful than dose response models because BBDR consider time-dependent changes of concentration.[13]

There are many advantages for the models, determining internal doses rather than administered doses and key metabolites allows for a more direct relationship with the response additionally using ADME , pk, and PD properties permits route to route and species to species (e.g.animal to human).[13]

There are number of disadvantages PK and PD parameters may be unavailable or inaccurate. In such cases the parameters are estimated using in vitro to vivo or species to species , the same problems applies when using animal studies to estimate pk and PD parameters for modeling toxicity in humans.[13]

PBPK was used for route-to-route extrapolation of toxicity and risk assessment and carcinogenicity assessment.[13]

Bioinformatics

Bioinformatics involves the collection, storage, analysis and retrival of data (usually biological data) for the use of that data in the production and optimization of the drug molecule. Target identification, drug screening and refinement can be accelerated with the help of bioinformatics and it also facilitate in determining side effects and predict drug resistance.[14]

High - through put data obtained from bioinformatics such as genomic, epigenetic, genome architecture, cistromic, transcriptomic, proteomic, and ribosome profiling data have all made significant contribution to mechanism - based drug discovery and drug repurposing.[14]

Determination of biological structures and development of homology modeling and protein structure simulation, coupled with large structure databases of small molecules and metabolites, have given the way for more enhanced and realistic protein-ligand docking experiments and more informative virtual screening. Conceptual framework that drives the collection of these high-throughput data, summarize the utility and potential of mining data in drug discovery, outline a few inherent limitations in data and software mining these data, point out new ways to refine analysis of diverse types of data. Few examples of

bioinformatics aided experimental approaches are listed below.[14, 15]

1. Determination of protein, DNA, and RNA sequences.
2. Searching for related sequences in other organism sequences.
3. Searching of functional patterns in proteins and nucleic acids.
4. Determine if there is any known interaction among proteins and other molecules.
5. Structural studies and predictions.
6. Managing data.[14, 15]

Homology modeling

It also known as comparative modeling of protein. It makes atomic model of target protein from its amino acid sequence and an experimental 3D structure of a related homologous protein(template). This technique actually identifies the structures of protein which are similar to the target protein or its sequence of amino acids. The sequence alignment and template structure can then be used for the production of the target protein model. This is followed by the assessment of the model.[16]

Homology Modelling process[16]

1. Identification of the template protein structure residues with the target sequence required.
2. Alignment and confirmation.
3. Target protein model development.

Protein data bank (PDB)

It is a data base for 3D structural data of proteins and nucleic acid. Thus with the help of this data target structure is easily determined which helps in the development of lead. The lead is so developed that it binds only to the target of interest avoiding all others and this results in the minimization of the toxicity of the drug. Thus the toxicity can be first accessed and then minimized even before the development of drug. This data is mainly obtained from X-Ray crystallography and sometimes from NMR. This data is available on internet through organizations such as PDBe, PDBj, RCSB and BMRB. It is looked and managed by an organization known as, World Wide Protein Data Bank. X- Ray diffraction gives approximations of the coordinates of the atoms of protein while NMR gives distance between the pair of the atoms of protein. Final confirmation of the protein is achieved by NMR. X-Ray crystallography also gives electron density map of proteins.[17]

Process of protein data entry in PDB[17]

Research data of protein----> Validation----> Protein Data Bank Entry.

Softwares

Table 3: Softwares used for toxicity prediction. [17, 18]

Name of software	Prediction
TOPKAT	Carcinogenicity and skin sensitization, etc. (2D QSAR)
EDKBD (Endocrine descriptor knowledge-based database)	Binding affinity of compound with nuclear receptor.
ADMET predictor	ADME and toxicity.
MolCode Toolbox	ADME
T.E.S.T(Toxicity estimation software tool)	Drug induced developmental toxicity.

DISCUSSION

Predictive toxicology is toxicity testing method, done with / without animals. Non animal methods are generally referred to as in silico methods. By this method we can predict the molecular structure, pharmacokinetics and pharmacodynamics properties through which we can know the bioavailability of compounds as well as their toxicity. This method uses data collection and analysis techniques and structural data generation and comparing techniques, some practical techniques and some data analysis techniques to accurately predict the toxicity of new compounds. Thus, these in – silico techniques are widely used for the design and development of new drug to increase its efficacy.

CONCLUSION

In-silico techniques are the methods which uses softwares for the prediction of a particular compound with respect to its properties and are also used for the structural determination of compounds and thus are used for toxicity determination. In – silico methods like QSAR, docking and other methods are very efficient and accurate for determination of compounds and their properties from their structures. Bioinformatics also gives us hint of toxicity of our compound which is slightly/highly similar to the reference compound already present in the database. By studying in-silico methods like QSAR, HQSAR, docking, PDB and several other methods and comparing it with in-vivo and in-vitro methods as given in table no. 1, the conclusion comes out to be that, in-silico methods of predictive toxicology are more better than in-vitro and in-vivo methods since they are much more safe(as animals are not harmed), economic, fast and accurate w.r.to, results/output in predicting toxicity of compounds by computational methods and hence are widely used in the production of new drug for accessing its toxicity.

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