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EVALUATION THE EMERGING ROLE OF *IN-SILICO* OPEN SYSTEM PHARMACOLOGY (OSP) AND ARTIFICIAL INTELLIGENCE (AI) BASED PHARMACOKINETIC TOOLS IN THE DEVELOPMENT OF PHARMACEUTICAL SCIENCES AND MEDICINES

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ABSTRACT

Artificial Intelligence is tremendously growing and improving day by day in drug development. New AI techniques used for disease detection and diagnosis include machine learning (ML) and deep learning (DL). To design and simulate pharmacokinetic-pharmacodynamic (PK-PD) models of medications and their effects on the human body as well as drug development, users can now use Open Systems Pharmacology, an AI-based software tool. MoBi and PK-Sim are both come under OSP tools. In all phases of preclinical and clinical drug development as well as health risk evaluations, the mathematical modeling technique known as physiologically-based pharmacokinetic (PBPK) modeling is employed. Pharmacokinetics can be applied to medicine to calculate the best drug dosage and timing schedules. Recently PBPK modeling particularly focuses on the application to the treatment of cancer. The systems pharmacology database and analytic platform for traditional Chinese medicine (TCMSP) was developed using this approach. It includes 499 Chinese herbs, 29,384 constituents, 3,311 targets, and 837 related disorders. In order to predict ADMET, drug-drug

interactions, drug-likeness screening, physicochemical properties, pharmacophore modeling, and the blood brain barrier penetration property of any medications quickly and accurately, users have access to a variety of AI-based pharmacokinetic tools. There are plenty of them, including (1) PKQuest, (2) SwissADME, (3) admetSAR, (4) OSIRIS, etc. Every tool is available online and has an intuitive user interface. Most of them are free to use, while some have paid or commercial version also along with free version. However, due to privacy concerns, open source or free software is not commonly utilized in the research and development (R&D) and pharmaceutical industries. The aim of this review is based on in-depth current information about a few AI-based pharmacokinetic tools and how they can accurately and efficiently estimate pharmacokinetics & pharmacodynamics within pharmaceutical compounds.

Keywords: PK-PD, Artificial intelligence, ADMET determination, OSP, ADMET software, Pharmacokinetic tool, Drug interaction

1. INTRODUCTION

The term " artificial intelligence" (AI) is a general term that refers to a branch of computer science that simulates human intelligence and decision-making processes using mathematical models and algorithms without significant human intervention **[1]**. The time-consuming and expensive process of drug discovery includes disease selection, target identification, lead finding and optimization. Only a few drug candidates have actually reached to the market over the previous 10 years due to the high percentage of clinical trial failures. The two main reasons for these failures are their pharmacokinetic inefficiency and toxicity. These days, AI is tremendously helpful for finding novel medicines quickly and improve pharmacokinetic properties. It is a useful tool for researching the SARS-CoV-2 and learning about its traits, pathogenicity, and genome and development of COVID-19 **[2]** therapy and research **[3, 4]**. Today's algorithmic machine learning (ML) and deep learning (DL) methodologies are two examples of modern AI techniques, that are also employed for identifying and diagnose a wide range of illnesses, including Alzheimer's **[5–7]**, cancer **[8–12]**, diabetic retinopathy **[13–18]**, chronic heart disease **[19–22]**, tuberculosis **[23–25]**, stroke **[26–28]**, and other cerebrovascular disease and natural language processing for illness symptoms and prognosis and also been used in a number of drug discovery processes, including peptide synthesis, structure-based virtual screening, toxicity prediction, drug monitoring and release, pharmacophore modeling, QSAR, drug repositioning, poly pharmacology, and physiochemical activity **[29–31]**. One example of employing AI for

disease detection is the IDx-DR gadget **[32]**, which uses a fundus retinal camera with an AI algorithm to detect diabetic retinopathy **[33]**. Several benefits of AI are included: Reduced human mistake, availability around-the-clock, implementation of risks rather than populations, quick decisions, reduced time consumption and Artificial Intelligence (AI) has some drawbacks to develop and implement: AI is highly expensive because it needs the most up-to-date software and hardware to run in order to stay current requirements. The inability of AI to think freely and independently is a serious problem in the technology **[34, 35]**.

Pharmacokinetics, in general, is the prediction of a substance's time-dependent concentrations in a biological system. A computational process known as physiologically based pharmacokinetic (PBPK) modeling **[36, 37]** uses mathematical equations to simulate the absorption, distribution, metabolism, excretion & toxicity (ADMET) of a substance in the body of an organism based on the interactions among important physiological, biochemical, and physicochemical factors **[38, 39]**. A significant benefit of PBPK modeling is the availability of a detailed structural description of an organism's physiology. The parametrization of PBPK models **[40]** takes into account of both the physiological and anatomical information about the organism and the drug's substance-specific features It is common practice to use PBPK models to assess metabolite distribution and forecast the likelihood and severity of drug–drug interactions, based on 15 substrate PBPK models submitted by nine sponsors between 2009 and 2013, this assessment was made. There was a total of 26 DDI investigations (cases) using different CYP inhibitors for these 15 models **[41]**.

Open System Pharmacology (OSP), also known as a Physiologically based Pharmacokinetic (PBPK) model. There are many Pharmacokinetic tools available that can accurately and quickly predict the ADMET features of any medication. These are (1) PKQuest, (2) SwissADME, (3) admetSAR, (4) OSIRIS, (5) molinspiration cheminformatics, (6) pkCSM, (7) Edsim++, (8) ADMETlab 2.0, (9) preADMET and many other.

2. OPEN SYSTEM PHARMACOLOGY (OSP)

A group of AI software tools called Open System Pharmacology (OSP) **[42]** enables users to create and simulate **PK-PD**[1] models of pharmaceuticals and their effects on the human body depending on *in vitro* and *in vivo* data **[43, 44]**. The body's processes for

[1] **PK-PD**: Pharmacokinetic-Pharmacodynamic

ADME of medications, as well as their interactions with biological targets to produce therapeutic effects, are described by PK-PD models **[43, 44]**. A community called Open Systems Pharmacology is dedicated to creating, validating, and disseminating expert freely available software models and tools for simulation and design in the pharmaceutical sciences. It seeks to offer trustworthy, strong, and simple modeling and simulation tools for use in the pharmaceutical and other life sciences. The scientific profession, including academics, regulatory bodies, and business, accepts and values the Open Systems Pharmacology community. One potential method to improve the information gained and the effectiveness of the decision-making process during drug development is the expanded application and integration of PK-PD concepts in all stages of preclinical and clinical drug development **[45, 46]**. The OSP Suite is available to everyone without charge. One type of AI tool for assessing the ADMET effects and cytochrome P450 3A4 (CYP3A4) dependent drug-drug interaction of medications in people is the Open Systems Pharmacology suite **[47]**, which also includes building PBPK models for medicines and calculating pediatric trial dosages based on physiology. OSP tools like PK-Sim and MoBi are used to build PBPK models, which replicate drug ADMET in the body. These models can be used to assess the efficacy and safety of medications, for the intended purpose of predicting CYP3A4-mediated drug-drug interactions (DDIs) and improve dosing regimens **[48]**. For pediatric **[49]** studies, the suite provides physiology-based pharmacokinetic dosage estimations with high levels of predictability **[50]**. Users can directly download OSPSuite-Full.11.2.187.exe [*https://github.com/Open-Systems-Pharmacology/Suite/releases/download/v11.2/OSPSuite-Full.11.2.187.exe*].

3. OPEN SYSTEM PHARMACOLOGY TOOL

3.1 PK-Sim

PK-Sim is a comprehensive piece of software for modeling pharmacokinetics over the entire body **[51]**. The PK-Sim is created and maintained by the Open Systems Pharmacology project. It is used to estimate the pharmacokinetics (PK) of drugs in both people and animals. A building block concept is used by PK-Sim to enable simulation organizing. Individuals, Populations, Compounds, Formulations, Administration Protocols, Events, and Observed Data are the different building blocks of PK-Sim. It offers easy access to all relevant anatomical and physiological parameters for humans as well as data on the most common pre-clinical animal models (mouse, rat, minipig **[52]**, dog, and monkey). The sophisticated modeling

software program MoBi is also totally compatible with PK-Sim. These are the interstitial space, blood vessels, plasma, and cellular space. Under specified exposure settings, juvenile PBPK models make it easier to estimate pharmacokinetic (PK) parameters in children. PK-Sim is useful for forecasting parameters of PK and their variation in children as well as for locating crucial system-specific inputs **[53]**. These models can be used to facilitate the selection of small molecule medication doses for pediatric patients. Benefits of using PK-Sim for pediatric PBPK modeling include: Mechanistic, physiology-based modeling has shown excellent performance in describing and predicting PK in children. OSP Suite 11 Update 2 and the most recent variation of PK-Sim, 11.2.142, were made accessible.

3.1.1 MODEL DESCRIPTION IN PK-SIM

3.1.1.1 PBPK model for preparation of monoclonal antibody in Pediatrics

A software program used for PBPK modeling of monoclonal antibodies **[54]** is called PK-Sim. Utilizing PK-Sim, monoclonal antibody PBPK models for juvenile populations can be created and includes 15 organs or tissues for modeling monoclonal antibodies in pediatric patients. These are the interstitial space, blood vessels, plasma, and cellular space etc. These models can be used to facilitate the selection of small molecule medication doses for pediatric patients. Benefits of using PK-Sim for pediatric PBPK modeling include: Mechanistic, physiology-based modeling has shown excellent performance in describing and predicting PK in children. For pediatric studies, the suite provides physiology-based pharmacokinetic dosage estimations with high levels of predictability **[55, 56]**.

3.1.1.2 CYP3A4 based Drug interaction

A widespread software system for PBPK modeling is PK-Sim, and various research have utilized it to forecast DDIs caused by CYP3A4. Typically entail creating PBPK models of both the responsible drugs (i.e., the medicine that impacts CYP3A4 activity) and the victim medication (i.e., the medication whose metabolism is impacted by CYP3A4 inhibitions or stimulation) and modeling their pharmacokinetic characteristics in various circumstances **[57, 58]**. These PBPK models may be applied to evaluate the effectiveness and safety of medications, for the sole purpose of recognizing drug-drug interactions (DDIs) caused by cytochrome P450 3A4 (CYP3A4) **[59]** and improve dosing regimens **[60, 61]**. These models, which ranged from potent CYP3A4 induction to potent inhibition, were coupled with the appropriate CYP3A4

DDI victim medications. With **MATLAB**[2] **[62, 63]** and **R**[3] **[64–66]** functions, it is possible to employ optimized codes for PK-Sim **[67]**. The effectiveness of the PBPK models as predictors is then assessed by comparing the accuracy and reliability of these simulations to clinical data. Overall, CYP3A4-mediated DDIs may be predicted using PBPK modeling utilizing PK-Sim, which is a promising method that can assist in clinical and drug development decision-making **[68]**.

3.1.1.3 PBPK model for protein

The PBPK model for proteins was developed as an expansion of the small molecule drug PBPK model used in the PK-Sim software. The PBPK model for small molecules has distinct blood pool compartments and 15 organs or tissues. The endosomes and lysosomes found inside vascular endothelial cells were represented by an additional compartment for each organ. Lysosomal degradation and **FcRn**[4] binding with a high affinity are both seen in this endosomal space compartment. The model explicitly depicts cellular space because it was created from a PBPK model for small molecule medicines **[69]**.

3.1.2 FUNCTION

A few of PK-Sim's functions are listed below:

3.1.2.1 Simulation: Simulations in PK-Sim can be completed rapidly after creating at least one building block for People, Compounds, and Administration Protocols.

3.1.2.2 Compounds: The transcellular specific permeability of the gut wall is estimated. The plasma protein binding in young infants will be scaled using the ontogeny function. A drug's predominant binding site, albumin or alpha1-acid glycoprotein can be determined using PK-Sim.

3.1.2.3 Formulations: Based on the Noyes-Whitney technique, PK-Sim can determine the dissolution kinetics of spherical particles with a known particle size distribution. Using PK-Sim, users can simulate drug compositions and their impact on drug release.

[2] **MATLAB:** Matrix laboratory is the meaning behind the name. For technical computing, MATLAB is an excellent performance language. An advanced matrix/array language with facilities for objects-oriented programming, input/output, data formats, control flow instructions, and input & output.

[3] **R:** R is a computer programming language designed by statisticians primarily for using with data in statistics. It's an algorithm used to compute statistics and visualize data.

[4] **FcRn:** A human gene called FCGRT encodes the protein known as FcRn. It is an antibody-binding receptor that aids in the transmission of IgG across the mother towards the fetus and in the body's recycling of the substance.

3.1.2.4 Gene expression data: To calculate the in vivo activity of enzymes and transporters that affect drug metabolism and transport, PK-Sim uses gene expression **[70]** data.

3.1.2.5 Tools and Variables: Physicochemical information and plasma protein binding are two examples of the tools that PK-Sim offers. It also determines variables for each organ, such as partition coefficients and permeability surface area products.

3.1.2.6 GIT absorption model: models that already exist commercially and are based on physiology and explain the process of gastrointestinal absorption **[71]**. The stomach to the rectum is separated into 12 compartments for the GI tract in the absorption model used in PK-Sim **[72]**.

3.1.2.7 Oral absorption model: The small intestine is included as a single, continuous compartment with spatially changing features in the 'plug-flow-with-dispersion' **[73–75]** model of oral absorption **[76, 77]** used in PK-Sim.

3.1.3 ADVANTAGES

A computer program called PK-Sim is used to model whole-body pharmacokinetics (PBPK). The following are some benefits of utilizing PK-Sim:

3.1.3.1 Computational based generic structure: The PBPK software program PK-Sim, which is a component of the Computational Systems Biology Software Suite, is based on a generic structure with 18 organs and tissues and fully integrates absorption, distribution, metabolism, and excretion in a single model **[78–80]**.

3.1.3.2 Flexibility: It offers a lot of flexibility along with the user-friendliness of PBPK modeling software backed by a graphical user interface (GUI) **[80]**.

3.1.3.3 Prediction of drug interaction and dose adjustment: Predicting the effects of drug interactions **[81]** and dosage changes on a drug's pharmacokinetics is achievable with PK-Sim. This can help to optimize pharmacological therapy and prevent unwanted side effects.

3.1.3.4 Reusability: When modeling various substances, PK-Sim offers reusable building pieces that can save time and effort.

3.1.3.5 Automatic processes: PK-Sim automatically considers relevant specific active processes, such as metabolization by a specific enzyme, as well as applicable generic passive processes.

3.1.4 DOWNSIDE

- A number of input parameters used by PK-Sim in the construction of its models are derived from measurements, databases, and assumptions.
- Model adjustments are limited to minimal ones in PK-Sim, which is intended for non-expert users.
- When it is extremely high and the organ is getting close to blood, a definite clearance value may not be obtained.

3.1.5 AVAILABLE WEBSITES AND SERVERS

Users can obtain the most recent changes and source code on GitHub and the website of Bayer Technology Services, where they can download [*https://pk-sim.software.informer.com/download/*] and [*https://github.com/Open-Systems-Pharmacology/PK-Sim/releases*] the software.

3.2 MoBi

MoBi is a software program for multiscale physiological modeling and simulation in system biology. A current method for interspecies translation of monoclonal antibody (mAbs) employing open-source software (PK-Sim and MoBi) is the (mAbs) pharmacokinetics (PK) in the context of target-mediated drug disposition (TMDD) **[82]**. MoBi is employed in the modeling and simulation of quantitative systems pharmacology (QSP) and physiologically-based pharmacokinetic (PBPK) processes. MoBi is an open-source product, which means anyone can use it for free. MoBi also enables the combination of the aforementioned instances, making it a very potent tool for modeling and simulating multi-scale physiological systems that span both whole-body architecture and molecular specifics on the one hand. The scientific potential of MoBi OSP is fascinating to diabetes experts. It can be used to create systems pharmacology PD models as well as PBPK models of blood glucose, insulin, and glucagon. These models can aid in understanding the processes of glucose metabolism as well as the implications of various therapies on the management of diabetes. Building blocks used by MoBi are categorized as Molecules, Reactions, Spatial Structures, Passive Transports, Observers, Events, Initial Conditions, Parameter Values, and Observed Data. MoBi provides preset structural objects, including as organs, compartments, linkages, and reactions, for model development. It can simulate interacting PBPK models for numerous substances at once. In a graphical working environment, MoBi's structural objects enable the hierarchical structuring of models and the representation of the entire body, organ, tissue, and subcellular level. A broad variety of physiological models can be

made with MoBi, including but not limited to:

- Models for pregnant women that are Physiologically Based Pharmacokinetic.
- Physiologically based models of pharmacokinetics throughout the body.
- Drug-dynamic models.
- Models of how diseases develop.
- Models for metabolite.
- Model toxicity.

3.2.1 DIFFERENCE BETWEEN PK-Sim AND MoBi

With MATLAB **[83]** and R functions, it is possible to employ optimized codes for PK-Sim. The following are some variations between PK-Sim and MoBi.

3.2.2 ADVANTAGES

The following are some benefits of MoBi OSP (Open Systems Pharmacology):

3.2.2.1 Versatility: A systems biology software package called MoBi OSP enables the import of many biological model types, including PBPK (Physiologically Based Pharmacokinetic) models, compartmental disease progression models, and biochemical reaction networks.

3.2.2.2 Rescue of building blocks: Building blocks, which are already-made parts that can be reused in the creation of models, are used by MoBi OSP.

3.2.2.3 Combination of models: Biochemical reaction networks and PBPK models, for example, can be combined with other types of models using MoBi OSP to create a single simulation.

3.2.2.4 Graphical tools: MoBi OSP offers graphical tools to help experienced users create and simulate models. These tools improve user experience and speed up model creation.

4. OPEN SYSTEM PHARMACOLOGY FOR HERBAL DRUGS (TCMSP)

The concept of systems pharmacology for herbal medicines served as the foundation for the development of the Traditional Chinese Medicine Systems Pharmacology database and analytic platform (TCMSP) **[84]**. TCMSP is a cutting-edge pharmacology platform for Chinese herbal medicines that establishes connections between drugs, disease targets, and many sorts of illnesses. The database contains information on substances, targets, drug-target network, drug-target related disease networks, as well as pharmacokinetic properties for natural substances that take into consideration oral bioavailability, drug-likeness, intestinal permeability to epithelial cells, BBB, water solubility, and others. The Chinese Pharmacopoeia lists 499 Chinese herbs; TCMSP includes specifics on these

plants as well as information on 29,384 ingredients, 3,311 targets, and 837 illnesses they are linked to. The recently created TCMSP offers current, quantitative, and systems information about the components of TCM, as well as information regarding diseases, targets, and ADME-related features. One article in SPRINGER LINK[84] on licorice, one of the oldest and most widely used herbal medicines in the world, was published. This case will demonstrate how to use TCMSP for screening active components, identifying drug targets, and diagnosing illnesses. Three crucial areas are where TCMSP shines out: (1) Establishing relationships between compounds, targets, and diseases to allow for in-depth studies on TCM theory, mechanisms of action, and drug discovery. (2) The incorporation of massive structural information (29,384 chemicals along with 13,144 distinct molecules) and manually adjusted data for all herbs listed in the Chinese Pharmacopoeia. (3) Including 12 important ADME-related features that were obtained from various sources. The TCMSP consists of 2387 target-disease combinations and approximately 84260 or more compound-target pairs. Twelve essential ADME-related metrics have been provided for screening of drugs and assessments, involving human oral bioavailability, half-life, drug-likeness, Caco-2 permeability, blood-brain barrier, and Lipinski's rule of five. The three main categories of TCMSP are as follows: (1) Compounds, targets, and disease information (2) Herbal components with their qualities connected to ADME (3) Relationships between targets and compounds, as well as diseases and targets.

5. DIFFERENT PHARMACOKINETIC TOOLS

5.1 PKQuest

A free Java-based software program called PKQuest is used to model physiologically-based pharmacokinetics (PBPK). The Java-written tool can be downloaded for free from (*https://www.pkquest.com/assets/docs/PKQuest_11.15975715.zip*). The results for PKQuest do not include a commercial version. PKQuest has a number of features, including a user-friendly PK and graphical software with integrated Physiologically Based Pharmacokinetic (PBPK).

5.1.1 FEATURES OF PKQuest

There are numerous unique elements in PKQuest, many of which have never been used in a PBPK before. These are described below:

- It is a Java-based software program called PKQuest is used to model physiologically-based pharmacokinetics (PBPK).
- PKQuest is a user-friendly, interactive software program that is free to download.

- PKQuest now offers graphical display. No user input is necessary to select the routine graphical output because it is displayed in graphical form by default **[85]**.
- Enflurane, nitrous oxide, halothane, methoxyflurane, and toluene are just a few of the volatile solutes whose pharmacokinetics have been modelled using PKQuest **[86]**.
- A new general-purpose PBPK software procedure called PKQuest was previously utilized to simulate the pharmacokinetics of propranolol **[87]** in humans.
- It contains a lot of characteristics, that determines the rate of gastrointestinal, intramuscular, intraperitoneal, or cutaneous absorption and systemic availability of a medicine using plasma concentrations **[87]**.
- To reduce the amount of user input, PKQuest offers a "*Standardhuman*" and "*Standardrat*" data collection **[87]**.
- The use of PKQuest in studies of human ethanol **[88]** pharmacokinetics will reveal details regarding the First Pass Metabolism (FPM), the timing of intestinal absorption, and the total quantity of ethanol that reaches the liver.
- PKQuest was created using the Maple (version 6,7 & 8) computer algebra system, (*www.maplesoft.com*) the user must have Maple installed and operational in order to use it **[89]**.
- Every system with Maple installed should be able to run PKQuest, which is accessible for the majority of operating systems (PC, Mac, and Linux).
- The values of "fclear" must match those of the other parameters, hence PKQuest is the first PBPK model to include both permeability and plasma protein binding **[90]**.
- To simulate the drug concentration-time profiles **[91]** in various tissues and physiological compartments, researchers can enter drug-specific parameters into PKQuest, such as dose, mode of administration, and drug characteristics. This data can be used to optimize drug dosing regimens **[92]**.
- The pharmacokinetic features of several medications into the model, PKQuest can be used to simulate and assess drug-drug interactions **[93]**.
- A variety of pharmacokinetic parameters, including clearance, volume of distribution, and half-life for diverse medications obtained by PKQuest.

5.1.2 AVAILABLE WEBSITE AND SERVER

The Java-written tool can be downloaded for free from [*https://www.pkquest.com/assets/docs/PKQuest_11.15975715.zip*] or [*http://www.pkquest.com/program/pkquest_program.zip*].

5.1.3 GUIDELINES BEHIND INSTALLATION

PKQuest.zip should be unzipped. It is crucial that the "lib" folder and the pkquest.jar file stay in the same folder, which is called the "dist" folder. To run PKQuest, double click the "jar" file. To view the D2O PBPK example, click the "Run" button.

5.1.4 LIMITATIONS

- This need might make PKQuest less accessible to those who don't have access to or aren't familiar with Maple.
- The kinetics of highly lipid-soluble and extracellular solutes, as well as the primary unpredictability and constraint of PBPK analysis, can impair the accuracy of the data obtained by PKQuest.

5.2 SwissADME

The Molecular Modeling Group of the SIB (Swiss Institute of Bioinformatics) is the organization responsible for the SwissADME program. The free online application SwissADME enables users to assess several small molecule characteristics relevant to pharmacokinetics, drug-likeness **[94]** and medicinal chemistry friendliness. The findings for SwissADME don't have a commercial version. It offers computer models to calculate important physicochemical characteristics and molecular attributes. SwissADME is a component of the ambitious SwissDrugDesign program, which aims to create cutting-edge computational approaches for examining the characteristics of small molecules.

5.2.1 FEATURES AND ADVANTAGES OF SwissADME

- Pharmacokinetic parameters (ADME) **[95, 96]** for tiny compounds including blood-brain barrier permeability, intestinal absorption, and P-glycoprotein substrate potential and physicochemical parameters including molecular weight, logP, polar surface area, and hydrogen bond donors and acceptors can be computed using SwissADME.
- SwissADME can evaluate a small molecule's drug-likeness **[96, 97]** by comparing its characteristics to those of existing medications.
- Blood-brain barrier permeability, which may be a sign of possible

neurotoxicity, can be predicted by SwissADME.

- Furthermore, SwissADME is capable of computing a number of physicochemical parameters of small compounds, including molecular weight and polar surface area, which are useful for predicting toxicity potential.
- Small compounds' compatibility with medicinal chemistry **[98]** is evaluated by SwissADME.
- SwissADME is made to be simple to use and open to a wide range of users, including those with no prior knowledge of computational chemistry or cheminformatics.
- SwissADME has been applied to the drug discovery and also for design and creation of anticancer **[99–101]**, antitubercular **[102–104]**, and antibacterial **[105]** medicines **[106]**.
- The phytochemicals and bioavailability of phytochemicals found in herbal plants are also predicted using SwissADME **[107–109]**.
- In order to do ligand-based target estimation for any biologically active micro molecule, SwissTargetPrediction is an internet-based app that has been available online since 2014. Inexperienced users are protected from methodological traps and arduous technical tasks by the user-friendly graphical interface **[110]**.

5.2.2 PARAMETER PREDICTION BY SwissADME

There are different parameters that SwissADME can check **[111]**. These are described below:

5.2.2.1 SwissADME as Lipophilicity determination

N-octanol and water's partition coefficient (log Po/w) is the conventional definition of lipophilicity. This physicochemical property has a unique area in SwissADME because of its crucial importance for the pharmacokinetics drug discovery process. SwissADME offers access to five open-source prediction models, including XLOGP3, an atomistic model with knowledge-based library and corrective factors, WLOGP, an original execution of a pure atomistic approach based upon the system of Wildman and Crippen fragmental, MLOGP, a prototypical topological approach based upon linear relations with 13 molecule-specific descriptors implemented and SILICOS-IT, a hybrid approach using 27 fragment and 7 topological descriptors. Another internal physics-based method is iLOGP, which uses the Generalized-Born and solvent accessible surface area (GB/SA) concept to calculate the free energy values of solvation in n-octanol and water.

5.2.2.2 Physicochemical properties

In this section, simple molecular and physicochemical characteristics including molecular weight, molecular refractivity count of particular atom kinds, and polar surface area (PSA) are compiled. Version 2.3.0 of OpenBabel is used to calculate the values. This has shown to be a helpful descriptor in numerous models and guidelines for rapidly assessing some ADME properties, particular in relation to biologic barrier crossing like absorption and brain permission.

5.2.2.3 Water Solubility

SwissADME has two topological strategies for predicting the solubility in water; the first is based on the ESOL model, while the second is based on work. SILICOS-IT created the third solubility predictor for the SwissADME. The linear correlation coefficient of this fragmental technique, modified for molecular weight, is R^2=0.75. SwissADME offers these units along with qualitative solubility classes, solubility is in mol/l, and solubility is in mg/ml.

5.2.2.4 Pharmacokinetics:

The Pharmacokinetics section compiles the predictions of specialized models that investigate particular ADME behaviors of the medication under investigation **[112]**. The predictions for passive human gastrointestinal absorption (HIA) and BBB permeability are made possible by the display from the BOILED-Egg model, an understandable visual categorization model, that can be shown in the SwissADME result web page by tapping the red hyperlink that appears under the sketcher after all input compounds have been processed. SwissADME enables the identification of chemicals as either P-gp substrates or inhibitors of the most important CYP iso-enzymes.

5.2.2.5 Graphical Output

Once all calculations have been completed, the red "Show BOILED-Egg" button manifests underneath the sketcher and displays the graphical output. The BOILED-Egg, an intuitive method for concurrently estimating two critical ADME properties, namely passive gastrointestinal absorption (HIA) and brain access (BBB), makes up the majority of this. For all compounds submitted to SwissADME, predictions are included in the graphical output. In a variety of drug development scenarios, the BOILED-Egg has shown efficient molecular design translations along with simple interpretation.

5.2.3 LMITATIONS OF SwissADME

There are several restrictions to the use of SwissADME. A few SwissADME's drawbacks are listed below:

5.2.3.1 Accuracy: SwissADME has been verified and demonstrated to be reliable for a few applications, its predictions might not always be correct for all compounds or uses. Its predictions' accuracy is based on how well-made the models and algorithms are.

5.2.3.2 Applicability: SwissADME is intended to assess small compounds, drug development and medicinal chemistry hence it might not be applicable for bigger molecules and predictions might not be applicable to other fields.

5.2.3.3 End Points: Comparatively to other programs like FAF-Drugs4 and admetSAR 2.0, SwissADME only supports a few endpoints. For instance, SwissADME covers 12 physicochemical features, 10 medicinal chemistry endpoints, and 9 ADME endpoints.

5.2.4 AVAILABLE WEBSITE AND SERVER

5.2.5 Quick and simple data input and interpretation are guaranteed by a simple user interface with login-free webpage. [*http://www.swissadme.ch]* Users can check more, various parameters from: [*https://www.expasy.org/resources/swissadme].*

5.3 AdmetSAR

A comprehensive resource and free tool for predicting and evaluating chemical ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties is admetSAR **[113]**. The old version of admetSAR, which had 27 predictive models, was released in 2012; however, it has since been modified to admetSAR 2.0 in 2018, which includes 47 models accessible for drug discovery or environmental risk assessment. It offers a collection of curated information for various compounds linked to known ADMET characteristics. The admetSAR prediction models do not appear to contain any evidence of recognized biases. admetSAR has two prediction option one is normal prediction of ADMET poperties, where users can insert only one SMILES of one compound at a time and another is advanced predict where users can insert upto ten SMILES of different compounds at a time.

5.3.1. IMPROVEMENTS OF admetSAR TO admetSAR 2.0

By improving the pre-existing models and adding multiple new ones with more training data, the system was updated to the latest version, 2.0. Notably, the optimal alternative for each model, as determined by training with a range of deep learning algorithm and molecular fingerprinting, has been selected for each model. Additionally,

developed a program called ADMETopt2 that automatically enhances a questionnaire molecule's ADMET characteristics using transformation rules and scaffold hopping[5]. AdmetSAR 2.0 serves as a framework for lead optimization and ADMET estimation in drug design. The framework and user interface were also modified for user comfort.

5.3.2 FEATURES / ADVANTAGES OF admetSAR

There is no cost to use admetSAR.

5.3.2.1 Prediction of properties: The database has quantitative regression models with good prediction accuracy as well as qualitative categorization models that enable the assessment of ecological/mammalian ADMET features for novel compounds. There were deployed 47 highly prospective qualitative categorization models altogether (version 2, 2018). These are including human intestinal absorption, Caco-2, blood brain barrier, P-glycoprotein inhibitor, CYP substrate (3A4, 2C9, 2D6) and inhibition (3A4, 2C9, 1A2 etc), carcinogenicity, eye irritation, reproductive, respiratory and nephrotoxicity, honey bee toxicity etc.

5.3.2.2 User friendly interface: The user-friendly interface of admetSAR makes it simple for users to look up chemical information by its CASRN (CAS Registry Number), common name, or structure **[114]**.

5.3.2.3 Curation of data: Over 96,000 distinct compounds contain over 210,000 ADMET analyzed data points that were carefully chosen from a wide range of literatures for admetSAR. 45 distinct types of ADMET-associated traits, proteins, and species are present in these substances **[114]**.

5.3.2.4 Extensive models: having 27 predicted models since its initial publication in 2012. A variety of predictive models are available from admetSAR in 2012, and admetSAR 2.0 in 2018, offers 47 models for drug development and environmental risk assessment **[115]**.

5.3.2.5 Conjunction with other tools: To better comprehend the ADMET properties of compounds, admetSAR can be used in conjunction with other tools like pkCSM and vNN-ADMET. ADMETlab 2.0 **[116]** is a comprehensive online platform that contains admetSAR, pkCSM, and vNN-ADMET, among other tools.

[5] **Scaffold hopping:** One method for identifying structurally new molecules is known as scaffold hopping, often known as lead hopping. By changing the molecule's central core structure, scaffold-hopping techniques often begin with known active substances, ending through a novel chemotype.

5.3.2.6 Physicochemical property calculation: Small molecular physicochemical property computations are essential for computationally screening their "drug-likeness" and "lead-likeness" and toxicity potentials. The five conventional physicochemical characteristics of log P, topological polar surface area (TPSA), molecular weight (MW), and acceptance of hydrogen bonds and donors were calculated for each compound in admetSAR using OpenBabel v2.3.1 **[117]**.

5.3.2.7 Creation of computer models: 22 qualitative model classifications were implemented in admetSAR utilizing the support vector machinery classification approach and an internal substructure pattern recognition technique. In addition, the supporting vector machine regression algorithm was used to create and implement five quantitative regression models. MACCS keys generated with OpenBabel v2.3.1 were used to represent every compound during the model development process **[118]**.

5.3.3 LIMITATION / DRAWBACK

This model has several limitations. The following list of admetSAR predictive model drawbacks is provided:

5.3.3.1 User Interface: admetSAR's user interface might not be as user-friendly as those of other ADMET programs.

5.3.3.2 Accuracy: The caliber of the data utilized to train admetSAR's models may have an impact on the predictability of its results. It's not entirely accurate. admetSAR was able to predict some ADMET features with high accuracy, but it was less accurate for others, according to one study.

5.3.3.3 Limited applicability: Some chemicals may not be suitable for admetSAR. admetSAR might be ineffective at predicting ADMET features for specific molecules, such as peptides and macrocycles.

5.3.3.4 Limited number of compounds: The constrained selection of substances accessible for testing is another drawback of admetSAR.

5.3.4 AVAILABLE WEBSITE AND SERVER

The admetSAR tool is accessible at [*http://lmmd.ecust.edu.cn/admetsar2/*].

5.4 OSIRIS

The complete name of OSIRIS is Open Source Independent Review and Interpretation System. The tool is freely usable and accessible online. It aids in assessing the likelihood of unfavorable consequences of chemicals under investigation. Multiplex short tandem repeat

(STR) DNA profiles can be evaluated using the public domain quality assurance software program OSIRIS. In order to evaluate the raw electrophoresis data stored in .fsa or .hid files, OSIRIS develops a mathematically based scaling technique separately. OSIRIS now supports the ABI capillary analysis and RAPID DNA analysis platforms.

5.4.1 IMPORTANT CHARACTERISTICS

- A free computational program called OSIRIS **[119]** can be used to forecast the pharmacokinetic characteristics of potential medication candidates.
- The relevant features of medications in the preclinical stage are assessed by OSIRIS using in silico technology.
- It provides real-time drug-relevant property calculations and enables users to create chemical structures, such mutagenicity or insufficient intestinal absorption.
- High-risk characteristics are displayed in red, whereas drug-conformant behavior is displayed in green. Red is used to highlight properties that pose a significant risk of adverse effects including mutagenicity or poor intestinal absorption, while green denotes drug-conformant behavior.
- It can determine drug scores, molecular weight, drug-likeness indices, logS for solubility in water, and logP for lipophilicity **[120]**.
- Numerous applications of OSIRIS are possible, such as automating reanalysis, automating fragment analysis, stem cell engraftment testing, forensic casework, kinship analysis, expert systems, cell line verification, and monitoring lab processes **[121]**.
- Different pharmacokinetic features of drug candidates can be predicted by the OSIRIS tool. These are including Intestinal absorption, penetration of the blood-brain barrier, CYP450 blockage, Mutagenicity, Carcinogenicity, Acute toxicity, Skin hypersensitivity, endocrine disruption **[122]**.

5.4.2 OSIRIS PROPERTY EXPLORER

While creating pharmaceutically active molecules, it is important to optimize the physicochemical and toxicological molecular characteristics, which can be predicted using the free tool Property Explorer. Actelion Pharmaceuticals Ltd. published the original version of Osiris Property Explorer in 2000 under the domain name www.actelion.com. It was created by T. Sander. When a chemical structure is

valid, the tool allows you to draw it and instantly calculates a number of attributes that are pertinent to drugs. The outcomes of the prediction are rated and color-coded, with red denoting features with a high likelihood of undesirable effects as mutagenicity, carcinogenicity or poor absorption in the intestines and green designating properties that behave in accordance with the medicine. It has become the accepted practice for predicting physicochemical properties and toxicity risk. Users can download the .jar file from [*https://www.organic-chemistry.org/prog/peo/peo.jar*].

5.4.3 AVAILABLE WEBSITE AND SERVER

This program is easily downloadable by users from URL: [*https://www.ncbi.nlm.nih.gov/osiris/download/*].

5.4.4 SOFTWARE NECESSITIES

System must have a functioning Java Runtime Environment (JRE) installed. Users can install the most recent JRE from [*https://java.com/en/download].*

6. CONCLUSION

The previous section provided a review of Open Systems Pharmacology (OSP), which is composed of PK-Sim and MoBi, and various pharmacokinetic tools, are AI-based software tool for the most current studies that used PK-PD models of drugs and pharmaceutical substances in human and animal bodies on in vitro-in vivo data. There are available to assess the ADMET characteristics, drug-drug interactions, lipophilicity, physical qualities, pharmacodynamic features of pharmaceutical compounds and are now also very helpful in drug development and dosing regimens without using animals in preclinical trials. Reducing the utilization of animals, time, as well as cost is the main goal to use these programs. Today, the use of AI for disease diagnosis, identification, and dose selection is rapidly growing. In this evaluation, we tested various Physiologically Based Pharmacokinetic (PBPK) software and went into great detail regarding the current situation. PK-Sim is utilized in paediatrics to simulate monoclonal antibodies and determine whole body pharmacokinetics. System biology modelling and simulation at multiple scales benefit from MoBi. On the other side, direct open access to SwissADME website for ADMET and determining physical properties by drawing structure and after Canonical SMILES insertion. OSIRIS Property Explorer and admetSAR, a tool for determining toxicity, by using green and red colour. SwissADME has additional capabilities that enable it to anticipate BBB crossover behaviour from “BOILED Egg” structure. All the softwares are very much

useful and not taking extra time to give results and has user friendly interface. In future the use of these tools will be more to reduce the use of animal in pre-clinical trials and These software will be more updated and more fast.

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