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In silico approaches which are used in pharmacy

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ABSTRACT

This mini-review theoretically illustrates the *in silico* methods used in the pharmacy field to enhance drug discovery and development and reduce preclinical studies. It is shown that *in silico* methods are computational-based approaches that study the structure, properties, and activities of molecules using computer simulations and mathematical algorithms. These results highlight the importance of obtaining data that can affect the prediction of *in vivo* results. Artificial intelligence and machine learning development enhance *in silico* methods such as quantitative structure-activity relationship, molecular placement, and physiological-based pharmacokinetics, which are usually used. This approach not only saves time and costs but also offers ease of application. Studies conducted to evaluate the use of *in silico* methods in areas such as pharmacology, toxicology, and pharmaceuticals are provided as examples. It was concluded that over time, *in silico* methods usage and development increased due to their ability to predict the *in vivo* performance of the drug.

INTRODUCTION

Drug development studies consist of processes, that take a long time, and cost, furthermore, are not always successful *in vivo* trials [1,2]. The process of drug development timeline takes about 7–15 years for drug molecules to pass through various stages and become usable as drugs [3–5]. Moreover, drug development processes are complex stages that can be achieved as a result of cooperative studies in sciences such as chemistry, biology, and pharmacology [6]. To solve the problems that may be encountered, mathematical models have been developed that include *in vivo* and *in vitro* approaches and can evaluate physiological and pharmacological information together [7]. By using the developed *in silico* models, it is possible to reduce the time of drug development studies and costs [8–12].

In the pharmacy field, *in silico* tools have emerged as vital resources. One of the primary benefits of employing *in silico* approaches is their ability to predict drug properties according to the molecular structure [13]. In addition, they can predict absorption, distribution, metabolism, and excretion (ADME) properties [13,14], thereby reducing the need for extensive *in vivo* studies and leading to significant time and cost savings, ultimately accelerating drug production [15,16] by identifying and predicting the impact of drugs on biological systems, clinical use can be improved, side effects can be avoided, and treatments can be better selected and developed [17]. Several official authorities have recommended and even provided *in silico* tools for assessing chemicals in terms of hazard identification, risk assessment, and human health safety evaluation. Workflows have been established to guide the application of these *in silico* tools for chemicals risk assessment and computational toxicology [10].

When it comes to disadvantages, accurately predicting oral absorption and bioavailability using *in silico* methods can still pose challenges [18,19]. Some *in silico* software lack transparency in disclosing the underlying algorithms used for predictions. Despite recent advancements, there is still a gap in correlating *in vivo*, *in vitro*, and *in silico* ADME parameters [14].

In silico methods are applications based on calculating the properties of drugs (such as solubility and partition coefficients) and other chemical substances and their effects

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on the body with computer models [20–22]. These are applied using computer software at different stages in drug discovery and development. *In silico* methods include quantitative structure activity relationship (QSAR) methods which assess to evaluate the data arising from pharmacology laboratories. Molecular docking methods depend on drug and macromolecule interaction to provide atomic-level data. Quantum medicinal chemistry methods facilitate the assessment of the electronic structure and provide valuable insights into the chemical and biochemical processes related to drugs. Molecular dynamic methods are particularly helpful in modeling, exactly in fit effect of drug-macromolecule complexes. In addition, virtual screening efforts aid as a complementary technique to preclinical screening implementing on lead compounds. In the field of drug discovery, artificial intelligence methods are making significant progress and providing a significant number of innovative tools. Furthermore, the application of pharmacoinformatic techniques is highly demanded at each stage of the drug discovery and development process, including target identification, validation, 3-D structure prediction, medicinal and product chemistry, pharmacology (both *in vitro* and *in vivo*), pharmaceutics, formulation, drug delivery and disposition (pharmacodynamic and pharmacokinetic), preclinical and clinical trials, and postrelease study of drug-patient response. In the last years, these methods have gained increasing significance in certain fields, for instance, pharmacology, toxicology, and biotechnology [23]. This review aims to highlight the most common *in silico* method used in drug discovery and development.

IN SILICO CONCEPT

The term *in silico*, meaning "performed on computer or via computer simulation," is derived from the concepts of *in vivo* and *in vitro*. The United States Environmental Protection Agency (EPA) defines the term *in silico* as the "integration of modern computing and information technology with molecular biology to improve agency prioritization of data requirements and risk assessment of chemicals" [24,25]. The European Union defines it as data models obtained without testing and uses them in the risk assessment of chemical substances [26]. Computer-aided methods have many advantages such as predicting the biological activity of the drug based on its structural features, determining its efficacy and side effects before clinical studies, limiting the use of animal experiments, helping the rational design of safe drug candidates, repositioning marketed drugs, and facilitating the drug development process [27–30].

Identification and analysis of a new drug's efficacy, safety, toxicity, and drug specifications are very important in the drug discovery or formulation development stage. For this purpose, *in vitro* and *in vivo* experiments have been implemented for a long time. Due to the high use of experimental animals in *in vivo* studies, the high cost of these studies, and the long-time consumption. Scientists have sought alternative methods, leading to the widespread adoption of *in vitro* experiments utilizing invertebrates, cell cultures, and tissue-organ baths. Nevertheless, the demand for more efficient and ethical approaches continues to grow, prompting the development of *in silico* methods [31].

DATA SECURITY AND VALIDATION IN *IN SILICO* APPROACHES

External validation data sets and the diversity of the size and structure of the training data sets partially impact the estimated performance of *in silico* models [32,33]. *In silico* models and simulations are based on data obtained as a result of *in vitro* and *in vivo* experimental studies. Compliance and accuracy of these studies with scientific methodology are significant for the reliability of *in silico* methods [15]. According to the European Chemicals Agency (ECHA), the necessary steps for the reliability and acceptance of the data to be obtained by *in silico* methods should be carried out systematically and regularly. The procedures have been classified for *in silico* methods according to the Regulation of Registration, Evaluation, Authorization, and Restriction of Chemical Substances [34]. Details of this classification process are shown in Table 1.Applicability is an important factor in the validation of *in silico* methods. In other words, accurate predictions about physicochemical and structural properties and activity should be made by using a model or simulation. While determining this, an accuracy level is determined for the *in silico* method beforehand and when the method is applied to a chemical substance, it is analyzed mathematically and statistically whether it gives results at this accuracy level. In addition, parameters such as sensitivity and selectivity required for validation are also determined. While evaluating validation parameters in *in silico* methods, limiting factors such as data reliability, limited chemical substance groups, and applicability areas, in addition, the possibility that pharmacological and toxicological results may vary by different mechanisms should be considered in data analysis and evaluation studies [32].

IN SILICO METHODS

This section focuses on the most common *in silico* methods.

Structure activity relationship (SAR)

In 1868, Crum-Brown and Fraser suspected the quaternary ammonium character of curare [35]. Curare is a poison that causes muscle paralysis and blocks the action of the excitatory neurotransmitter acetylcholine on the muscle receptor. Analysis of its neuromuscular blocking effects in animals concluded that this physiological effect was the function of tubocurarine [36]. A little later, Richardson studied the increased hypnotic activity of aliphatic alcohols in relation to their molecular weight (MW). These studies formed the basis for the SAR model [37]. Currently, *in silico* modeling is employed for SAR analysis of pharmacological and toxicological activities. This modeling application involves a qualitative analysis of the chemical properties, as well as the biological and pharmacological effects of molecules. Functional groups, stereochemical structure, size and shape, chemical reactivity, resonance, and inductive effects are taken into account [38,39].

Quantitative SAR

In 1893, Richet noted the effect of physicochemical properties on pharmacological activity [40,41]. In the 1960s,

Table 1. Process steps determined by ECHA for the reliability of *in silico* method (according to [34]).

In silico evaluation steps	Actions to be taken
Step 0: Collection of information	Verification of parent compound structure, collection of information
	Scanning databases and identifying missing information
Step 1: Preliminary analysis	Examination of the reactivity of the parent compound
	Making the first evaluation after ingestion
Step 2: Using the classification schemes	Obtaining detailed information about the activity using classification schemes for the targeted impact
Step 3: Scanning specific points	Determination of specific structures and groups in the structure of the compound, if any, for the targeted effect
Step 4: Preassessment	Making a preliminary expert assessment of the expected reactivity and toxicity of the parent compound with the information obtained
Step 5: Screening for similar compounds	Selection of the compound responsible for the effect of the substance
	Determining whether the selected compound falls into the existing categories
	Evaluation of similarity with similar substances of the compound that does not fall into the existing categories
	Gathering information about identified similar substances
	Identification of similarities between the compound responsible for the selected effect and similar substances, if these similarities are limited, screening for new similar substances and updating the study matrix
Step 6: QSAR estimates	Estimating the effects of the compound with the QSAR, if no results are obtained, determining, and applying different QSAR models
Step 7: Final assessment	Making the final expert decision on both the parent compound and the other compounds responsible for the effect, using all the information obtained

Corwin Hansch showed the importance of the change in physicochemical properties that could lead to variation in biological activity (the structure-activity pattern) by examining certain structure modifications of the compounds [41,42].

The basis of the QSAR method is based on the tendency of structurally similar molecules to show similar biological activity. These models mathematically describe how the activity response of a target molecule that binds a ligand varies according to the structural properties of the ligand. QSAR is obtained by calculating the correlation between experimentally determined biological activity and various properties of ligand binders and is used to predict the activity of new drug molecule analogs. The success of a QSAR model depends on the molecular descriptors chosen and their ability to predict biological activity. The steps that take place in the QSAR model are as follows: active molecules that bind to the desired target molecule and their activities; database search or high throughput scanning result is defined. The number of bonds, atoms, functional groups, and surface area, that affect biological activity. After defining the structural or physicochemical molecular properties, a QSAR model is created between the biological activity and the defined properties of the drug molecules, and this model is used to optimize known active compounds to increase biological activity. Then, new optimized drug molecule activities are experimentally tested [43].

Machine learning approaches such as neural networks and support vector machine methods are used to construct QSAR models. Table 2 presents some of the machine learning algorithms used in some QSAR models [44].

QSAR models summarize the relationship between chemical structure and biological activity and predict the activities of new chemical molecules. Quantitative structure-property relationship (QSPR), in which a chemical property is defined as a variable, is a reliable statistical model for estimating the properties of new chemicals and analytical systems. Quantitative structure reactivity relationship, quantitative structure chromatography relationship, quantitative structure toxicity

Table 2. Machine learning algorithms are used in some QSAR models (according to [44]).

Name of software	Algorithms
R	Random forest, support vector machines, naive Bayesian, and artificial neural networks
libSVM	Support vector machines
Orange	Random forest, support vector machines, and naive Bayesian
RapidMiner	Support vector machines, random forest, naive Bayesian, decision tree, artificial neural networks, and k-nearest neighbors
Weka	Random forest, support vector machines, and naive Bayesian
Knime	Decision trees, naive Bayesian, and support vector machines
AZOrange	Random Trees, Support vector machines, artificial neural networks, and random forest
Tanagra	Support vector machines, random forest, naive Bayesian, and decision tree
Elki	k-nearest neighbors
Matlab	Support vector machines, artificial neural networks, naive Bayesian, decision tree, and k-nearest neighbors
TreeNet	Random forest
SciTegic Pipeline Pilot	Support vector machines, naive Bayesian, and decision tree

relationship, quantitative structure electrochemistry relationship, and quantitative structure bioavailability relationship are other approaches that can be given as examples [45–47].

Previous studies have reported that QSAR models are divided into six categories of QSAR dimensions based on their molecular descriptor [48–51]. Table 3 provides a brief overview of these categories. Among these dimensions, the 3D-QSAR approach, a ligand-based drug design method, has proven to be instrumental in designing novel compounds. Chavda and Bhatt [52] conducted a study using four different 3D-QSAR techniques, including comparative molecular field analysis (CoMFA), comparative molecular similarity indices analysis (CoMSIA), molecular hologram QSAR (HQSAR), and topomer CoMFA, to design new B-Raf inhibitors using 28 synthetic B-Raf inhibitors. CoMFA correlated biological activity with steric and electrostatic parameters, while CoMSIA associated biological activity with hydrophobic, hydrogen bond donor, hydrogen bond acceptor, steric field, and electrostatic parameters. HQSAR correlated biological activity with the structural part of each group and atom of the molecules, providing essential insights into the impact of atoms, stereochemistry, and fragments on biological activity. The topomer CoMFA, aimed at overcoming CoMFA limitations, divided molecules into fragments, generating a model directly correlated with the molecule's fragments. *N*-fold statistical validation yielded q^2, r^2, and r^2_{pred} values of 0.638, 0.969, and 0.848 in CoMFA, 0.796, 0.978, and 0.891 in CoMSIA, and 0.761, 0.973, and 0.852 in CoMSIA. For HQSAR analysis, statistical values were $q^2 = 0.984$, $r^2 = 0.999$, and $r^2_{pred} = 0.634$, with a best hologram length of 97. Topomer CoMFA showed a q^2 value of 0.663 and an r^2 value of 0.967. Contour map analysis of these 3D-QSAR techniques helped identify crucial features of purinylpyridine, facilitating the design of novel molecules as B-Raf inhibitors for melanoma cancer treatment [52].

Table 3. Groups of QSAR models according to their analysis capabilities (according to [48–51]).

QSAR techniques	Parameters used
1D-QSAR	Physicochemical parameters such as pKa, log P
2D-QSAR	1D-QSAR + structural, geometric, electrostatic, and thermodynamic parameters
3D-QSAR	2D-QSAR + electrostatic, steric, hydrophobic parameters, and hydrogen bonding properties
4D-QSAR	3D-QSAR + parameters related to conformations, protonation, and stereoisomers
5D-QSAR	Parameters related to conformational changes in 4D-QSAR + ligand-protein binding
6D-QSAR	Parameters related to 5D-QSAR + solvation models

Molecular dynamics (MD) simulation

MD simulation is a computational technique that calculates the forces between molecules and computes their motion through numerical integration. Starting with the positions of atoms from an identified crystal structure and randomly generated velocities, Newton's equations are used to calculate the positions and velocities of the atoms at small time intervals. Through iterative steps, the forces are recalculated, and the simulation progresses. After an equilibration period (thousands of steps), during which the system (install) reaches the desired temperature and pressure, a production period begins, storing the molecular history for later analysis [53,54].

MD simulations have three essential applications in biomolecular dynamics. First, they bring biomolecular structures to life, providing insights into their natural dynamics in solution over different timescales. Second, MD simulations yield thermal averages of molecular properties, allowing the calculation of bulk properties of fluids and free energy differences for chemical processes, such as ligand binding, using time-averaged molecular properties that approach experimentally measurable ensemble averages, based on the ergodic hypothesis. Third, MD simulations explore the thermally accessible conformations of a molecule or complex [55]. MD simulations are commonly combined with various experimental structural biology methods, such as X-ray crystallography, cryoelectron microscopy, nuclear magnetic resonance, electron paramagnetic resonance, and Forster resonance energy transfer [54].

Molecular docking

Molecular docking is a powerful technique that investigates how small molecules behave within the binding area of a target protein. As more protein structures are determined through X-ray crystallography or nuclear magnetic resonance, molecular docking has gained prominence as a valuable tool in drug discovery. It is now possible to perform docking against homology-modeled targets for proteins with unknown structures. Through docking approaches, the druggability of compounds as well as their specification against definite targets can be computed, aiding in lead optimization processes. Molecular docking programs use a search algorithm to iteratively evaluate the ligand's conformation until it converges to the lowest energy state. Subsequently, an affinity scoring function (ΔG [U total in kcal/mol]) is applied to order the candidate poses by summing the electrostatic along with van der Waals energies. In addition, the driving forces behind these interactions in biological systems strive for complementarity between both the shape and electrostatics of the binding area surfaces and the ligand or substrate [56]. This comprehensive approach facilitates the identification of potential drug candidates and their interactions with the target protein, thus supporting the drug discovery process. Until 2016, no molecular modeling study has been conducted on ionone-based chalcones for anti-prostate cancer activity. Popular QSAR methods such as CoMFA and CoMSIA use 3D information to identify sites on molecules that can be modified to create more specific ligands, while HQSAR uses fingerprints to highlight sub-structural features significant for biological activity. In addition, molecular docking analysis provides insights into ligand-receptor interactions. By combining 3D-QSAR and docking, a more comprehensive understanding of the structural features at the protein's binding area and protein-ligand interactions can be obtained to aid in the design of new potential molecules. The generated models in this study exhibited statistical precision with higher q^2 and r^2 values. The presence of bulky, negatively charged substituents with H-bond acceptors at specific positions increased the activity. Moreover, the hydrophobic property of the phenyl ring played a crucial role in the anti-cancer activities of ionone-based chalcones.

Table 4. *In silico* tools are used for drug discovery and development.

Tool Name	Type	Website	License	Web services/ Software
AutoDock Vina	Molecular docking	https://vina.scripps.edu/	Open-source (free)	Software
AutoDock CrankPep	Molecular docking	https://ccsb.scripps.edu/adcp/	Commercial-source (paid)	Software
LeDock	Molecular docking	http://www.lephar.com/software.htm	Open-source (free)	Software
Glide	Molecular docking	https://www.schrodinger.com/products/glide	Commercial-source (paid)	Software
FlexAID	Molecular docking	https://nrglab.github.io/	Open-source (free)	Software
MedChem Studio™	Screening/ligand design	https://www.simulations-plus.com/software/admetpredictor/medchem-studio/	Commercial-source (paid)	Software
MolScore-Antibiotics	Target prediction	http://www.pharmainformatic.com/html/molscore-antivirals.html	Open-source (free)	Software
PatchSearch	Target prediction	https://github.com/UCDvision/PatchSearch	Open-source (free)	Software
SwissTargetPrediction	Target prediction	http://www.swisstargetprediction.ch/	Open-source (free)	Web services
SEA	Target prediction	https://sea.bkslab.org/	Open-source (free)	Web services
CSNAP	Target prediction	https://services.mbi.ucla.edu/CSNAP/	Open-source (free)	Web services
The ChemProt 2.0	Target prediction	http://www.cbs.dtu.dk/services/	Open-source (free)	Web services
PASS Online	Target prediction	https://www.way2drug.com/PassOnline/pe.php	Open-source (free)	Web services
QSAR TOOKBOX	QSAR	https://qsartoolbox.org/	Open-source (free)	Software
Lazer	QSAR	https://lazar.in-silico.ch/predict	Open-source (free)	Software
Toxtree	QSAR	https://apps.ideaconsult.net/data/ui/toxtree	Open-source (free)	Software
VEGA	QSAR	https://www.vegahub.eu/portfolio-types/in-silico-models/	Open-source (free)	Software
EPI Suite™	QSAR	https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface	Open-source (free)	Software
OncoLogic™	QSAR	https://www.epa.gov/tsca-screening-tools/oncologictm-expert-system-evaluate-carcinogenic-potential-chemicals	Open-source (free)	Software
Derek Nexus	QSAR	https://www.lhasalimited.org/solutions/	Commercial-source (paid)	Software
HazardExpert	QSAR	https://compudrug.com/hazardexpertpro	Commercial-source (paid)	Software
The BfR DSS	QSAR	https://www.tandfonline.com/doi/pdf/10.1080/10629360701304014	Commercial-source (paid)	Software
TOPKAT	QSAR	https://www.sciencedirect.com/science/article/abs/pii/0027510794901252	Commercial-source (paid)	Software
MCASE and CASE Ultra	QSAR	https://multicase.com/	Commercial-source (paid)	Software
Leadscope	QSAR	https://www.instem.com/solutions/insilico/computational-toxicology.php	Commercial-source (paid)	Software
TerraQSAR™	QSAR	https://www.terrabase-inc.com/	Commercial-source (paid)	Software
ACD/Percepta	QSAR	https://www.acdlabs.com/products/percepta-platform/physchem-suite/	Commercial-source (paid)	Software
MolCode Toolbox	QSAR	https://genecode.com/	Commercial-source (paid)	Software
TIMES	QSAR	http://oasis-lmc.org/products/software/times.aspx	Commercial-source (paid)	Software
CQSAR	QSAR	http://www.biobyte.com/bb/prod/cqsar.html	Open-source (free)	Software
SeeSAR	QSAR	https://www.biosolveit.de/SeeSAR/	Open-source (free)	Software
RPBS Web Portal	QSAR	https://mobyle.rpbs.univ-paris-diderot.fr/cgi-bin/portal.py?form=PASS#welcome	Open-source (free)	Web services
GastroPlus® PBBM / PBPK	ADME toxicity	https://www.simulations-plus.com/software/gastroplus/	Commercial-source (paid)	Software
ADMET Predictor®	ADME toxicity	https://www.simulations-plus.com/software/admetpredictor/	Commercial-source (paid)	Software
MolScore-Drugs	ADME toxicity	https://www.fqs.pl/en/products	Open-source (free)	Software
PK-SIM®	ADME toxicity	https://www.open-systems-pharmacology.org/	Open-source (free)	Software
Simcyp™ PBPK	ADME toxicity	https://www.certara.com/software/simcyp-pbpk/	Open-source (free)	Software
Cyprotex	ADME toxicity	https://www.cyprotex.com/insilico/	Commercial-source (paid)	Software
ADMET Modeler™	ADME toxicity	https://www.simulations-plus.com/software/admetpredictor/admet-modeler/	Commercial-source (paid)	Software
IMPACT-F	ADME toxicity	http://www.pharmainformatic.com/html/impact-f.html	Open-source (free)	Web services

These findings led to the design of twelve new anti-prostate cancer compounds (predicted high activity) [57]. In another investigation, Shahzadi *et al.* [58] synthesized MgO-doped cellulose nanocrystal grafted poly acrylic acid (CNC -g-PAA) hydrogel for antibacterial and anti-cancer activities. The hydrogel demonstrated improved bactericidal tendencies against both Gram-negative and Gram-positive bacteria, and molecular docking analyses were performed to evaluate the interactions between the nanocomposite hydrogel and biomolecules. The hydrogel also exhibited reactive oxygen species production by photocatalysis and showed promising potential for controlled drug delivery, with successful loading of the model anticancer drug Doxorubicin. *In vitro* cytotoxicity analysis further confirmed the enhanced antitumor efficiency of the nanocomposite hydrogels, suggesting their potential as carriers for innovative biomedical applications [58]. Furthermore, Shahzadi *et al.* [59] investigated the antibacterial and anti-arthritic effects of CNC-g-PAA and CNC-g-PAA doped with CaO. Molecular docking analysis was also conducted to evaluate the binding interaction between the targeted proteins and the synthesized nano-biomaterials. The results demonstrated improved antitumor effectiveness of CNC-g-PAA and CNC-g-PAA/CaO, suggesting their potential as delivery vehicles for multifunctional biomedical applications. These findings highlight the promising prospects of hydrogels in the field of biomedical research [59].

EXPERT SYSTEMS

Most *in silico* methods are based on the knowledge of pharmacology and toxicology specialists. Information about the molecular structures of substances is often incomplete, or complex. For this reason, expert systems have been developed based on the explanation of different expert knowledge with various data processing methods and algorithms, as seen in Table 4. One such software is SAR which was created by combining QSAR and data banks and mathematically expresses the rules for a chemical molecule. The most important advantage of the QSAR method is that it can be evaluated with a specific mechanism when needed [39].

Sample applications of *in silico* methods

Computer-aided tools have proven to be greatly effective within the healthcare industry. They have been used in the development of distinctive molecules that have successfully demonstrated their therapeutic potential in clinical trials for various disorders. Some remarkable examples of the uses of computer-aided tools in the development of approved drugs include an angiotensin-converting enzyme (ACE, captopril) inhibitor used in cardiovascular diseases treatment and prevention, which was approved in 1981 as well as carbonic anhydrase inhibitor (dorzolamide) used for treating glaucoma and approved in 1995. In addition, saquinavir (approved in 1995), ritonavir, and indinavir (both approved in 1996) were approved as medications for the treatment of human immunodeficiency virus (HIV) in accordance with safety regulations [60]. Other examples can be found in Table 5.

AutoDock Vina

AutoDock Vina is a freely available software used for conducting molecular docking. The program was initially developed and implemented by Dr. Oleg Trott at The Scripps Research Institute's Molecular Graphics Lab, which is now known as CCSB [61].

AutoDock CrankPep or ADCP

ADCP (AutoDock for peptides) is a specialized docking engine based on AutoDock, specifically designed for docking peptides. It combines techniques from the protein folding area with an effective representation of a rigid receptor using affinity grids. The process involves folding the peptide within the energy landscape obtained by the receptor, optimizing the interaction between the peptide and the receptor through a Monte–Carlo search, as a result, docked peptides are obtained. The program can handle peptides (3-D structures) within Protein Data Bank files or in the form of a sequence string [62].

LeDock

LeDock is a specialized software designed for fast, precise, and flexible docking of molecules into a protein. It has been shown to achieve a pose-prediction precision of over 90% on the Astex diversity group. For drug-like molecules, it typically takes about 3 seconds per run, making it a time-efficient tool. LeDock has been successfully utilized in high-throughput virtual screening campaigns, leading to the discovery of novel kinase inhibitors and bromodomain antagonists. One of its key features is its ability to directly use the SYBYL Mol2 format as input for small molecules [63].

FlexAID

FlexAID is an advanced docking algorithm capable of handling both small-molecules and peptides as ligands, with proteins/nucleic acids serving as targets. Its notable features include accommodating full ligand and target side-chain flexibility, adding versatility to the docking simulations. The scoring function employed by FlexAID is unique in its soft nature, reducing reliance on specific geometric criteria and instead focusing on surface complementarity. To fine-tune the scoring function's energy parameters, a substantial dataset containing native and near-native conformations (less than 2Å root mean square deviation) of almost 1,500 complexes from the PDBbind database was used as true positive examples. Remarkably, it has demonstrated superior predictive capabilities compared to well-established software such as AutoDock Vina and FlexX when predicting binding poses. This superiority is especially evident in cases where target flexibility is essential, as often encountered when applying homology models [64].

MedChem Studio™

MedChem Studio™ represents a comprehensive cheminformatics software bundle, encompassing a wide range of tools for essential drug discovery and development tasks, including high throughput screening analysis, prioritization, lead identification, *de novo* design, lead optimization, and scaffold hopping. An attractive feature is the "VIEWER" mode, which does not require a license and facilitates collaboration among scientists with different expertise. In addition, the software offers MedChem Designer™, a valuable molecular drawing tool, freely accessible from MedChem Studio. It

Table 5. Drugs developed by computer-aided approaches (according to [96]).

Drug	Target	Therapeutic use	Year of FDA approval	Reference
Erdafitinib	Fibroblast growth factor receptors	Urothelial carcinoma	2019	[97]
Dacomitinib	Multi-kinase	Nonsmall-cell lung cancer (NSCLC)	2018	[98]
Vaborbactam	Beta-lactamase	Bacterial infections	2017	[99]
Grazoprevir	NS3/4 serine protease	Chronic hepatitis C (HCV)	2016	[100]
Lifitegrast	LFA-1/ICAM-1 (leukocyte function-associated antigen-1/intercellular adhesion molecule1)	Dry eye disease	2016	[101]
Rucaprib	Poly (ADP-ribose) polymerase	Prostate cancer	2016	[102]
Saroglitazar	Peroxisome proliferator activated receptor	Diabetic dyslipidemia	2013	[103]
Telaprevir	NS3/4A protease	Chronic hepatitis C	2011	[104]
Rivaroxaban	Clotting factor Xa	Deep venous thrombosis	2011	[105]
Crizotinib	Anaplastic lymphoma kinase and ROS proto-oncogene 1	NSCLC	2011	[106]
Boceprvir	Hepatitis C virus (HCV)	Chronic hepatitis C	2011	[107]
Tomudex	Thymidylate synthase	Colorectal cancer	2009	[108]
Maraviroc	C-C chemokine receptor type 5/envelope glycoprotein GP120 (CCR5/gp120)	HIV	2007	[109]
Ambrisentan	Endothelin-A	Pulmonary arterial hypertension	2007	[110]
Aliskiren	Angiotensinogen	Blood pressure	2007	[111]
Sunitinib	VEGF-R2 kinase	Kidney cancer	2006	[112]
Darunavir	Nonpeptidic HIV-1 protease	HIV infection	2006	[113]
Getifinib	GFRv tyrosine kinase	NSCLC	2003	[114]
Zolmitriptan	5-hydroxytryptamine (5HT)1B/1D/(1F) receptor	Migraine	2003	[115]
Valsartan	Angiotensin II receptor	Hypertension	2002	[116]
Imatinib	Abl tyrosine kinase	Acute lymphoblastic leukemia	2001	[117]
Eptifiatide	Glycoprotein IIb/IIIa protein	Myocardial infarction	2001	[118]
Oseltamivir	Influenza A and B neuraminidase	In the treatment of the infection caused by the flu virus (influenza A and influenza B)	1999	[119]
Amprenavir	HIV protease	HIV infection	1999	[120]
Tirofiban	Integrin (GP) IIb/IIIa and Fibrinogen receptor	Heart attack	1999	[121]
Efavirenz	Non-nucleoside reverse transcriptase protein	HIV infection	1998	[122]
Delavirdine	HIV reverse transcriptase protein	HIV infection	1997	[123]
Nelfinavir	HIV-1 protease protein	HIV infection	1997	[124]
Ritonavir	HIV-1 protease inhibitor	To treat HIV infection	1996	[125]
Indinavir	HIV-1 protease	HIV infection	1996	[126]
Saquinavir	HIV-1 protease	HIV infection	1995	[127]
Dorzolamide	Carbonic anhydrase	Glaucoma and cystoid macular edema	1994	[128]
Cladribine	Adenosine deaminase	Hairy cell leukemia	1993	129]
Epalrestat	Aldose reductase	Diabetic neuropathy	1992	[130]
Flurbiprofen	Cyclooxygenase-2	Nonsteroidal anti-inflammatory agent	1988	[131]
Norfloxacin	Topoisomerase II and IV	Urinary tract infections	1986	[132]
Captopril	ACE	Hypertension	1981	[133]

grants users the ability to input or modify structures, visualize metabolites, define structure queries, and offer other valuable functionalities to enhance the software's versatility [65].

MolScore-Antibiotics

MolScore-Antibiotics serves as a valuable tool for distinguishing between antibiotics and nonantibiotics. This scoring system assigns a probability value between 0 and 1 to a compound, indicating the likelihood of possessing antibiotic activity. With its capability to assess compounds' potential antibiotic properties, MolScore-Antibiotics proves beneficial in guiding the process of selecting compounds for focused biological screening, particularly in prioritizing compounds from extensive collections. Our expert system's analysis demonstrated that many compound databases

from external suppliers have a limited number of compounds with antibiotic activity. As a result, MolScore-Antibiotics enables efficient cherry-picking of interesting antibiotic compounds, as exemplified in the selection of antibiotics from a database consisting of 195.064 compounds [66].

PatchSearch

PatchSearch is an innovative tool designed to facilitate the identification of potential off-target proteins by searching for structurally conserved binding sites across the entire surface of a protein. This powerful method employs a quasi-clique approach, allowing for a flexible consideration of binding area atoms without imposing overly strict distance conservation constraints. In essence, PatchSearch identifies dense subgraphs, or quasi-cliques, on the protein surface [67].

SwissTargetPrediction

SwissTargetPrediction offers a range of unique capabilities. First, it allows users to integrate 2-D and 3-D similarity values with known ligands. Second, the tool delivers results for five distinct species, enabling researchers to explore drug-target interactions across different organisms. Finally, SwissTargetPrediction permits users to map predictions based on target homology, facilitating the transfer of target predictions within and between organisms. These exceptional features make SwissTargetPrediction a valuable asset in drug discovery and target identification research [68].

Similarity ensemble approach (SEA)

The SEA employs ligand-based chemical similarity to establish relationships among proteins. This method enables quick searching of extensive compound databases and the creation of cross-target similarity maps [69].

Chemical similarity network analysis pull-down (CSNAP) web

CSNAP is a computational technique used to identify compound targets through network similarity graphs. By placing query and reference compounds on the network connectivity map, a graph-based neighbor counting method ranks the consensus targets within the neighborhood of every query ligand. CSNAP proves valuable in high-throughput target drug discovery as well as off-target prediction for compound sets obtained from either phenotype-based or cell-based chemical screens [70].

ChemProt-2.0

ChemProt-2.0 is a publicly accessible compilation of several chemical-protein annotation resources, enriched with diseases and clinical result information. This updated database now includes over 1.15 million compounds plus 5.32 million bioactivity measurements of all these for 15,290 proteins. Each protein is associated with quality-scored human protein–protein interaction information, comprising more than half a million interactions, which facilitates the study of diseases and biological outcomes through protein complexes. Notably, ChemProt-2.0 integrates therapeutic effects and adverse drug reactions, offering insights into proteins linked to clinical results. To enhance its functionality, the database employs new chemical structure fingerprints computed using the SEA [71].

QSAR toolbox

The toolbox is a user-friendly and free software application designed to facilitate reproducible plus transparent chemical hazard evaluation. It provides various functionalities, including the retrieval of experimental data, simulation of metabolism, and profiling of chemical properties. This valuable information and tools enable users to identify structurally and mechanistically known analogs and chemical classifications, which can be utilized for read-across and trend analysis, effectively filling data gaps in hazard evaluation [72].

Lazar

Lazar is a valuable tool utilized for predicting the toxic properties of chemical structures. In addition, it employs the QSAR statistical approach to generate predictions for a query structure by utilizing a database of experimentally determined toxicity data. The Lazar software model has demonstrated impressive performance in external validation datasets, achieving an accuracy (86%) along with a sensitivity (78%) in the carcinogenicity test, while attaining a remarkable accuracy (95%) for the mutagenicity test [73].

Toxtree

Toxtree is a valuable and freely available QSAR tool designed to assess the Cramer class of a chemical compound and evaluate its relative toxic hazard. Toxtree is a collaborative effort between Ideaconsult Ltd. and the Joint Research Centre of the European Commission [74].

VEGA

VEGA places a strong emphasis on generating transparent, reasonable, reproducible, and verifiable data in its models. To achieve this, they have optimized a series of tools that establish connections between the outcomes obtained for the target chemical and those obtained for structurally related compounds. These tools facilitate a reproducible read-across procedure, which involves extracting required values for the target compound depending on identified values for similar substances. This read-across strategy is made possible through the implementation of independent algorithms that go beyond QSAR models. These algorithms take advantage of identifying similar compounds as well as analyze the importance of descriptors and fragments for the chemical of interest plus the associated compounds [75].

EPI Suite™

The QSPR models available in EPI Suite™ have found extensive application in predicting physicochemical characteristics and half-lives of chemicals, particularly for screening-level hazard evaluation. These models were developed based on property data obtained from training sets, primarily comprising anthropogenic chemicals, including persistent organic pollutants, organochlorine pesticides, personal care products, modern pesticides, and industrial chemicals [76].

OncoLogic™

OncoLogic™, developed in collaboration with the EPA's structure-activity team (SAT), is a unique knowledge-

based software. The SAT consists of globally recognized experts responsible for assessing the carcinogenic potential of newly developed chemicals within the United States or those imported for marketing purposes. The objectives behind creating OncoLogic™ encompass several key aspects: Offering industry-specific guidance on crucial elements for developing safer chemicals. Providing a comprehensive source of information for all stakeholders, explaining the rationale behind identifying potential cancer hazards associated with chemicals. Promoting research initiatives to bridge existing knowledge gaps in this field [77].

HazardExpert

CompuDrug's HazardExpert stands as a crucial software tool, enabling the initial estimation of toxic symptoms caused by organic compounds in both humans and animals. Notably, HazardExpert incorporates a robust model that considers the bioavailability of the compounds. Its predictive capabilities surpass human experts, delivering toxic effect estimations with remarkable precision. HazardExpert offers toxicity prediction for organic compounds on the basis of toxic fragments, with results provided for seven distinct toxicity classes, including oncogenicity, mutagenicity, teratogenicity, membrane irritation, sensitivity, immunotoxicity, and neurotoxicity. In addition, the software calculates bioavailability built on pKa and logP, as well as bioaccumulation. Users can further predict toxicity for metabolites [78].

The BfR decision support system (DSS)

The DSS developed by the German Federal Institute for Risk Assessment (BfR) aims to evaluate specific hazardous properties of pure chemical substances, which include skin and eye irritation and/or corrosion. Serving as a rule-based system, the BfR-DSS has significant applicability in the regulatory framework classification of chemical substances within the European Union [79].

TOPKAT

TOPKAT aims to predict chemical carcinogens, focused on its capability to foresee the carcinogenicity of chemicals examined by the National Toxicology Program. However, TOPKAT's performance proved to be inadequate when attempting to distinguish potential rodent carcinogens and noncarcinogens within the studied dataset. The TOPKAT database consists of identified carcinogens and noncarcinogens, and the software attempts to identify chemicals that are most "similar" to unidentified compounds. Nonetheless, when observing six examples, the chemicals deemed "similar" by the software exhibited no apparent connection to the chemical of interest concerning metabolism or mechanism of carcinogenicity [80].

MCASE and CASE Ultra

CASE Ultra is a computer-based toxicology software designed to detect structural alerts associated with toxicity through (QSAR) analysis. The (QSAR) models in CASE Ultra undergo validation following Organization for Economic Co-Operation and Development guidelines and are accompanied by QSAR model reporting format reports. The software provides models for various toxicological endpoints, including bacterial mutagenicity/ICH M7, genotoxicity, carcinogenicity, skin sensitization, acute toxicity, endocrine disruption, reproductive toxicity, developmental toxicity, cardiotoxicity, hepatotoxicity, renal toxicity, ADME, and ecotoxicity [81].

LeadScope

LeadScope is an innovative computer software that seamlessly connects chemical and biological data, providing medicinal chemists with a powerful platform to visualize and interactively investigate extensive collections of chemicals, their properties, and biological activities. Within the software, chemical structures are intelligently categorized into a vast taxonomy of recognizable structural features, encompassing functional groups, aromatic rings, and heterocycles. All of these structural elements are further combined with general substituents, representing the fundamental construction blocks of medicinal chemistry [82].

TerraQSAR™

TerraQSAR™ computer programs have been meticulously crafted to offer rapid and dependable assessments of both the biological effects and physicochemical properties of organic compounds. The program provides valuable output data, including computed effect or property values represented in pT (log1/C) and mg/l (for rat and mouse intravenous: mg/kg b.w.), as well as the MW of the compounds [83]. For those seeking accurate and efficient estimations, TerraQSAR™ proves to be a valuable tool in the field.

ACD/Percepta

ACD/PhysChem Suite comprises multiple prediction modules that deliver accurate assessments of physicochemical properties based on molecular structure. It enables the estimation of essential properties, such as aqueous solubility, logD, logP, pKa, boiling point, Sigma, and other molecular specifications, specifically for organic compounds. Users can examine the calculated outcomes using sorting and plotting tools, ensuring the reliability of predicted physicochemical values. Moreover, the suite facilitates investigations into QSPR, structural modifications, and lead optimization to achieve desired target profiles. To enhance the applicability to novel chemical space, predictors can be trained with experimental data. ACD/PhysChem Suite also accommodates custom models and in-house prediction algorithms, offering flexibility for diverse scientific applications [84].

MolCode toolbox

The Molcode toolbox is an exceptional computational expert system developed for rapid and reliable prediction of crucial biomedical and environmental properties of chemicals and materials. It relies on proprietary techniques that map compound properties onto extensive sets of molecular descriptors, which include thousands of descriptors derived from quantum chemical theory, meticulously considering the intricate spatial and electronic structures of molecules. Ahead of this computation, molecular mechanics is employed to perform a comprehensive conformational search of extensive compounds.

Using the Molcode toolbox, users have the flexibility to load their own compound structures, make adjustments to encoded compounds, or even create and optimize entirely new ones [85].

CQSAR

David Elkins initially developed the first program for data searching in 1970, but its usage was cumbersome due to the encoding of structures in the Wisswesser line notation and the requirement to use IBM cards, resulting in slow and inconvenient operations. Consequently, the current C-QSAR program is the result of over 35 years of continuous research and development. The program was expertly designed and authored by David Hoekman, incorporating the widely adopted simplified molecular input line entry system notation (originated by David Weininger) for entering chemical structures. In addition, it effectively employs the Merlin searching program [86].

Ressource Parisienne en Bioinformatique Structurale (RPBS) web portal

RPBS is a collaborative effort involving multiple teams, with the goal of providing exclusive services in the domain of structural bioinformatics through a single-entry point. The expertise offered spans from sequence and structure analysis to modeling of protein as well as the design of drugs. However, not all aspects are currently addressed on the RPBS server. The server itself encompasses a wide range of tools, meticulously designed to holistically cover diverse areas of structural bioinformatics. As of now, the P-server section is only partially functional. In addition, RPBS offers access to proprietary software developed by their teams. Among other RPBS tools, some are specialized in handling 3-D structures, namely SA-Search, employed for discovering structural similarities and relying on a structural alphabet plus Scit, used for comparison side-chain conformations. Furthermore, RPBS maintains different compilations of commercially achievable organic compounds that prove useful for conducting structure-based *in silico* testing experiments [87].

GastroPlus®

GastroPlus® is an advanced software designed for modeling and conducting simulations of various properties of drugs or chemicals. These encompass release rate, absorption, bioavailability, pharmacodynamics, and pharmacokinetics. The software is equipped to predict drug-to-drug interactions, effects on animals, and virtual patient populations. It also facilitates researchers in modifying pharmacodynamic models based on observed data and employing the fitted models to forecast pharmacodynamic changes resulting from alterations in drug or chemical dosage, dosage form, and dosing regimen. Moreover, GastroPlus® enables the creation of *in vitro–in vivo* correlations and predictions of absorption and systemic distribution/elimination for large molecules [88].

ADMET Predictor®

ADMET Predictor® is advanced computer software designed specifically for QSAR modeling of ADMET properties. It provides estimations for more than 140 ADMET properties, offering a comprehensive analysis of drug properties. The software allows users to build QSAR and QSPR models by applying both in-house and publicly available data sources through a proprietary software program. Its user-friendly interface facilitates easy manipulation and visualization of data [89].

MolScore-Drugs

Amidst the diverse array of structures found in marketed drugs, molecules exhibiting biological activity share frequent characteristics. Through a thorough analysis of these intricate drug patterns, they have developed an expert system capable of distinguishing between drugs and nondrugs. For instance, MolScore-Drugs near 0 signifies the lowest predicted probability, while MolScore-Drugs near 1 indicates the highest predicted probability with an interesting ADME-profile. This expert system is founded on a collection of robust models. Leveraging SARs, we can estimate the drug-like chemical space effectively. In addition, structure-property relationships derived from their in-house ADME/Tox-database enable the prediction of ADMET properties and identification of potential risks, ultimately reducing clinical failures [90].

PK-Sim®

PK-Sim® is an extensive software tool designed for all body physiologically based pharmacokinetic (PBPK) modeling. It offers quick access to all pertinent anatomical and physiological parameters for humans and animal models (the most common preclinical), including mouse, rat, minipig, dog, and monkey, from its integrated database. The software also provides access to various PBPK calculation methods, streamlining model building and parameterization processes. PK-Sim® automatically considers relevant generic passive processes. For example, distribution through blood flow and specific active processes, like metabolization by specific enzymes. While PK-Sim® is user-friendly and suitable for nonmodeling experts, it allows slight structural model adjustments. Unlike many other PBPK modeling tools, PK-Sim® provides varied model structures to cater to critical distinctions between small and large drug molecules. Most notably, PK-Sim® seamlessly integrates with the expert modeling software tool MoBi®, granting full access to all model details, extensive modifications, and extensions. This capability facilitates the creation of custom systems pharmacology models tailored to the challenges of innovative drug research and development [91].

Simcyp™ PBPK

The Simcyp Simulator stands as the pharmaceutical industry's most complicated PBPK platform. Its capabilities encompass diverse applications, such as determining initial dosing for human trials, optimizing clinical study designs, assessing novel drug formulations, setting dosages for unstudied populations, and conducting simulated bioequivalence analyses besides foreseeing drug–drug interactions. Simcyp's versatility extends across small molecules, biological compounds, ADCs, generic drugs, and emerging modality drugs. By

linking *in vitro* to *in vivo* (ADME), as well as pharmacokinetic plus pharmacodynamic outcomes, Simcyp empowers the exploration of clinical scenarios and informed decision-making throughout drug development. Hence, Simcyp PBPK models offer comprehensive descriptions of drug behavior in tissues and organs. Every single organ can be represented by one or multiple physiological compartments. The drug concentration in each compartment is calculated through the integration of systems information, drug information, and trial design information [92].

Cyprotex

Cyprotex specializes in *in vitro–in silico* ADME-Tox services, covering a wide range of offerings. This encompasses *in vitro* ADME screening that aids discovery projects, as well as regulatory *in vitro* ADME and drug-drug interaction studies in the course of preclinical and clinical study and development. The company also provides specialized mechanistic *in vitro* human and animal toxicity models, such as 3-D models and MEA electrophysiology, along with PBPK and QSAR modeling expertise. Their comprehensive *in vitro* ADME and DMPK services contain metabolism studies, permeability and transporter assessments, solubility and physicochemical attribute evaluations, protein binding analysis, and pharmacokinetic and bioanalysis services. Cyprotex's data has been highly validated and trusted by over 1,700 clients across pharmaceutical, biotechnology, cosmetics, healthcare companies, academic, and government associations [93].

ADMET modeler

ADMET modeler serves as a valuable QSAR/QSPR model building within ADMET Predictor®. This module efficiently automates the challenging and time-consuming task of constructing high-quality predictions of QSAR and QSPR models using experimental data. Seamlessly integrating with ADMET Predictor, it takes advantage of the platform's descriptors as data and incorporates the chosen final model back into ADMET Predictor as an extra predicted property [94].

IMPACT-F

The assessment of oral bioavailability relies on robust computational models derived from the extensive PACT-F knowledge base, the largest repository of bioavailability data worldwide. Predicting human oral bioavailability early has numerous advantages, such as aiding in the selection of bioavailable drug candidates, and significantly reducing the risk of clinical failures compared to animal trials. The results are promptly available, ensuring confidentiality and reliability as no data or information leaves the company. Moreover, this approach enhances the potential of novel drugs by enabling a more precise determination of the optimal oral drug dose for first-in-human clinical trials. IMPACT-F, the novel expert system, is widely adopted by pharmaceutical companies across various therapeutic areas, including diabetes, inflammation, antivirals, autoimmune diseases, and cancer. It serves as a valuable tool for selecting and prioritizing drug candidates, optimizing prodrugs, and evaluating oral bioavailability before proceeding to clinical trials in humans. IMPACT-F stands out for its user-friendly interface, eliminating the need for chemical synthesis or animal experiments, and its superior reliability compared to animal trials, yielding immediate and crucial insights for future drug discovery and development. Ultimately, it plays a vital role in enhancing the efficiency and safety of human clinical trials [95].

DISCUSSION AND CONCLUSION

Drug discovery, development, and analysis studies involve a long and laborious process that requires time and high cost. The discovery of new drug molecules in the past; was done by examining the effects of molecules on known diseases through clinical observations, screening tests, and metabolism studies. Although this method was long and inefficient, it led to the discovery of many molecules until the 1980s. Studies for the development of new methods in order to increase the efficiency of the drug discovery, development, and analysis process and to achieve success in a short time with lower costs have yielded results. One of the alternative methods developed is *in silico* testing approaches based on computer simulations and mathematical algorithms.

In silico testing approaches, are approaches that limit the use of experimental animals used in *in vivo* experiments and reduce the time and cost required for the drug molecule to be marketed. Today, studies such as the discovery of the precursor compound and the optimization of the precursor compound are carried out through computer-assisted drug discovery and design. As a result of the rapid development of computational chemistry and biological sciences, computer-aided drug design methods continue to be successfully applied to accelerate the research and development process of drug molecules. With the development of artificial intelligence technology and machine learning, which are powerful data mining (DM) tools, the use of *in silico* methods such as QSAR, DM, molecular docking, molecular placement, and PBPK has increased. Due to *in silico* methods, which can be used in a wide variety of fields such as pharmacology, toxicology, cosmetology, and physiology, the discovery, preclinical analysis, and clinical studies of a drug molecule can be done easily. With these methods, the 3-D structures of drug molecules are examined, and their activities are estimated. The binding states of the ligand and the receptor are analyzed. Gastric and intestinal simulations are created with physiology-based pharmacokinetic models, and it is possible to examine the solubility, bioavailability, ADME, and toxicity properties of the drug. *In silico* testing approaches, there are disadvantages such as not always paying attention to pharmacokinetic properties and the possibility of obtaining erroneous results, but these methods have an important place in drug discovery, development, and analysis studies and are used progressively.

From the aforementioned introduction, it is easy to see that using *in silico* methods can be recommended for the prediction of a drug's *in vivo* performance through drug discovery or preformulation study, however, the used algorithms and data sets should be considered. Recently,

it was observed that the *in silico* research studies have increased, which contributed to the development of *in silico* modeling.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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