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Review

Section: Computational Biology

A Review of *In Silico* Toxicity Prediction

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HIGHLIGHTS

- Rapid Toxicity Screening
- QSAR and Read-Across
- AI-Based Toxicity Prediction
- Model Validation Challenges
- Integrated Toxicity Assessment

Key Words:
Toxicity
In silico toxicity
Machine learning
Artificial intelligence
Toxicological databases

ABSTRACT

Introduction: Toxicity assessment is essential in drug development, chemical safety evaluation, ecological monitoring, and regulatory decision-making. Conventional methods involving laboratory experiments and animal studies are time-consuming, expensive, and ethically challenging. In silico toxicity prediction provides a rapid, cost-effective approach for identifying potential toxicological risks. **Aim & Objective:** This review aims to describe the principles, methodologies, applications, advantages, limitations, and future perspectives of in silico toxicity prediction, emphasizing its role in improving safety screening and reducing experimental requirements. **Materials & Methods:** A narrative review was conducted examining computational toxicity assessment methodologies and their applications in pharmaceutical research and chemical safety evaluation. Major approaches included quantitative structure–activity relationship (QSAR) models, read-across methods, molecular docking, machine learning, deep learning, and systems toxicology frameworks. Their predictive capabilities, applications, and limitations were evaluated. **Results:** In silico approaches facilitate rapid toxicity screening, prioritization of potentially hazardous compounds, and prediction of adverse biological effects. QSAR models estimate toxicity using chemical structures, while read-across methods utilize information from structurally related compounds. Molecular docking investigates interactions between chemicals and biological targets. Machine learning and deep learning enable analysis of complex datasets and identification of toxicity-associated patterns. Integrating computational models with toxicological databases and mechanistic approaches may improve predictive performance. However, data quality, model interpretability, validation, and inadequate representation of biological complexity remain significant challenges. **Conclusion:** In silico toxicity prediction represents a promising approach to modern toxicological research, offering efficient and potentially cost-effective alternatives to conventional screening methods. Integrating artificial intelligence, reliable toxicological databases, and mechanistic modelling may enhance prediction accuracy and support next-generation risk assessment. Nevertheless, rigorous model validation and complementary experimental evidence remain essential for reliable safety evaluation and regulatory acceptance.

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INTRODUCTION

Drug development is an intricate process that involves scientific precision, commercial feasibility, and social implications, balancing the therapeutic effectiveness and safety standards of potential molecules [1]. Reports indicate that nearly 30 percent of preclinical candidate compounds fail to pass preclinical testing because of toxicity concerns, making negative toxicological responses the primary reason for drugs being pulled from the market [2, 3]. Toxicity refers to a drug's potential to harm cells. Toxicological tests are necessary for all chemicals used in medicine, beauty products, feed additives, environmental applications and the food industry. Traditional toxicity testing employs animal models to assess various effects, including acute, sub-chronic, chronic, carcinogenic, mutagenic, reproductive and ecotoxic effects. However, the high costs and complexities associated with these methods may render them impractical for evaluating all the synthetic and natural compounds in use today.

The advancements in computational algorithms have led to the development of *in silico* toxicity prediction, which utilises computer models to estimate the toxicity of substances prior to experimental evaluation. The United States Environmental Protection Agency (US EPA) defines *in silico* toxicology as the "*integration of modern computing and information technology with molecular biology to improve agency prioritization of data requirements and risk assessment of chemicals*" [4]. Regulatory bodies like the OECD, US EPA, the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), FDA, and European Chemicals Agency (ECHA) are becoming increasingly aware of these approaches, which are in accordance with the 3Rs concept (Replacement, Reduction, and Refinement of animal use) [5-8].

Overview of *in silico* toxicity prediction approaches

The fundamental concept is to convert chemical information into biological and toxicological predictions through computer analysis. This approach enables the identification of potential hazards before conducting extensive laboratory or animal research. To elaborate further on the topic, the first stage involves analysing the chemical structure. This analysis outlines the atomic structure and other chemical details that impact how living organisms function [9, 10].

Quantitative descriptors are derived from the structural information and encompass a vast array of physical and electrical attributes, such as molecular weight, hydrogen bonding, fingerprints, polar surface area, lipophilicity (log P), and more. Such computer representations serve as substitutes for traditional chemical representations [11].

The descriptors are put into action using various prediction approaches such as molecular docking, QSAR, read-across, machine learning, and others. The purpose of these models is to establish relationships between observed physiological or toxicological reactions and known chemical properties. The framework of the model enables the development of potential substance toxicity evaluations. Predictions may encompass a wide range of outcomes, including mutagenicity, carcinogenicity, hepatotoxicity, neurotoxicity, acute toxicity, ecotoxicity, among others [12].

Following that, the predicted danger is interpreted in connection with the dose, duration, method of exposure, and uncertainty aspects of the situation. This not only helps in determining the likely level of risk, but it also assists in the direction of subsequent experimental testing, prioritisation of chemicals, and making decisions about safety or regulatory concerns [13].

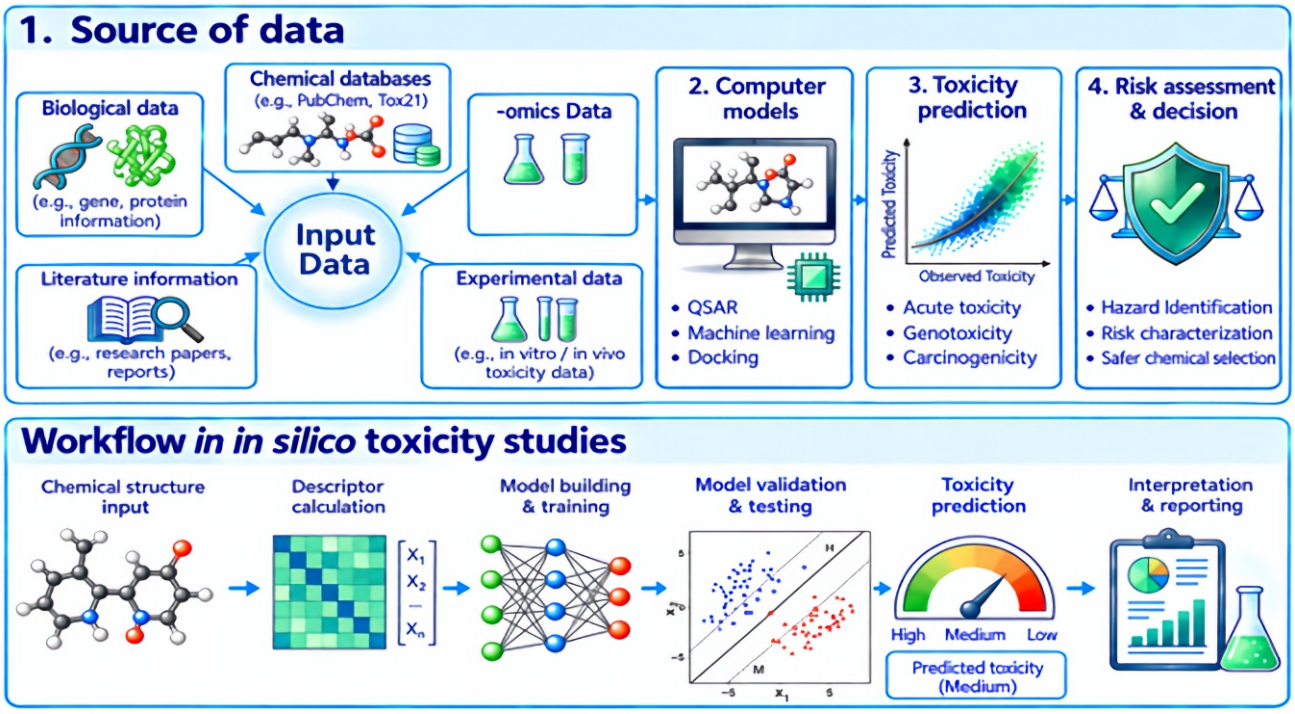


Figure 1: Showing the overall process for *in silico* toxicity prediction: 1) Types and methods to extract input data; 2) Types of computer models that can be implemented during the prediction; 3) Types of toxicity prediction such as acute, genotoxicity, and carcinogenicity; 4) Risk assessment and then decisions; 5) depicting how information from chemical structure can be used to estimate descriptors, then model building and validation, toxicity prediction and interpretation.

Major Computational Approaches

In silico toxicology encompasses many approaches that result in a wide variety of computational tools **(Figure 1)**: Databases, programs, modelling techniques, and visualisation tools are all part of the *in-silico* toxicology computational infrastructure. Chemical and toxicity databases contain data on chemical structures, physicochemical characteristics, biological activities, and experimentally determined toxicity. Chemical structures may be represented by numerical descriptors that capture crucial molecular and physical properties using molecular descriptor computing software. Molecular dynamics and systems biology are two methods that make use of simulation tools to study chemical interactions, biological systems, and dynamic processes. To predict various toxicological endpoints, toxicity modelling methods include QSAR, read-across, molecular docking, machine learning, and deep learning techniques can be used. Data analysis, model construction, validation, and prediction are all made easier by statistical and modelling tools. When it comes to toxicity prediction, expert systems use either web-based or standalone apps that contain pre-built models, rules, & algorithms. Molecular structures, interactions between molecules, biological networks, and computational findings may all be better understood and represented graphically with the use of visualisation tools. The tools included here provide a comprehensive computational framework that may be used for *in silico* toxicology tasks such as chemical characterisation, toxicity prediction, mechanistic understanding, and risk assessment [13, 14].

Quantitative Structure-Activity Relationship (QSAR) Models

Quantitative Structure-Activity Relationship (QSAR) models are computational methodologies that operate in order to create a mathematical link between the chemical structure or molecular characteristics of a substance and a certain biological or toxicological activity. These models are used to estimate the potential toxicity of chemicals that have not yet been exposed to experimental testing [15].

Function (f) is a mathematical equation or a machine learning model that establishes a connection between molecular characteristics and biological damage. The numerical values that are used to characterise the chemical, electrical, or structural characteristics of a molecule are called descriptors [16].

Common molecular descriptors

- *Hydrophobicity (logP)*
- *Molecular weight*
- *Topological indices*
- *Electronic descriptors*
- *Hydrogen bond donors and acceptors*
- *Molecular fingerprints*

Faster and cheaper than traditional experimental testing, *in silico* toxicity prediction has other benefits as well. Because of its efficiency in evaluating many compounds, it is ideal for screening huge chemical libraries. The regulatory screening process and the prioritisation of compounds for further investigation may both benefit from these methods. Nevertheless, *in silico* approaches do have certain restrictions. The amount, quality, and representativeness of the training data used to construct the prediction models greatly impact their dependability. Additionally, due to the fact that every model has a restricted application domain, the reliability of its predictions may decrease for chemicals that vary significantly from those used to construct the model. This means that these algorithms may not be able to properly forecast the toxicity of new chemical scaffolds if the training dataset doesn't adequately reflect them [17, 18].

Molecular Docking and Structure-Based Methods

Molecular docking is a computer simulation method to predict the interactions between biological macromolecules, typically proteins or nucleic acids, and small molecules, such as drugs or toxicants. This approach is essential in structure-based computational studies in molecular biology, toxicology, pharmacology, and drug development [19].

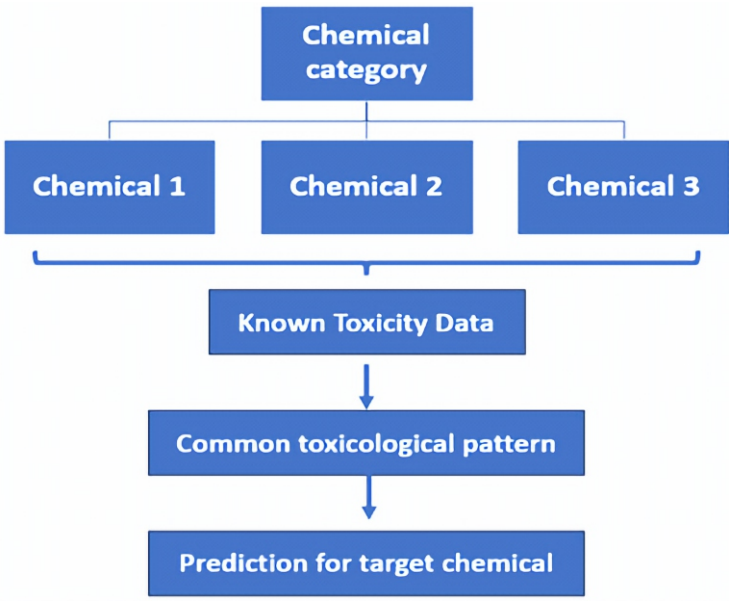


Figure 2: Showing principle read-across and chemical category approaches

Read-Across and Chemical Category Approaches

Read-across uses information from chemicals that are structurally or mechanistically related to forecast a target chemical's toxicity. This strategy is often employed by regulatory authorities in situations where experimental evidence is lacking [20].

Machine Learning Approaches

Machine learning (ML) has significantly advanced predictive toxicology by identifying complex nonlinear relationships between molecular characteristics and toxicological effects. There are two primary types of approaches: supervised and unsupervised:

Supervised Learning

In this method, the already known chemical toxicity results are used to train the model.

Common algorithms:

- Random Forest (RF)
- Support Vector Machine (SVM)
- k-Nearest Neighbours (k-NN)
- Decision Trees
- Logistic Regression
- Artificial Neural Networks (ANN)

Unsupervised Learning

When the chemical toxicity results are unknown, which means no predefined toxicity data, it relies on underlying patterns [21, 22]. Common algorithms:

- K-means clustering
- Hierarchical clustering
- Principal Component Analysis (PCA)
- Self-Organising Maps (SOM)

Toxicological Databases Supporting *in silico* Modeling

The success of computational toxicity prediction depends heavily on the availability of curated databases. **Table 1** shows some of the important resources for computational-based toxicity prediction.

Applications of *In Silico* Toxicity Prediction

In silico toxicology employs computational techniques like QSAR, read-across approaches, structural alarms, molecular modelling, machine learning, deep learning, and adverse outcome pathway (AOP)-oriented strategies to forecast the possible toxicity of substances. These methodologies may facilitate hazard identification [**Figure 3**], address data deficiencies, prioritise chemicals, and conduct risk assessments, all while reducing the necessity for extensive experimental trials [42, 43].

Prediction of Acute Toxicity

In silico methods can figure out how dangerous chemicals might be after a short-term or single exposure. To predict acute poisoning, two well-known approaches are QSAR and read-across. LD_{90}, LC_{90}, acute oral toxicity, dermal toxicity, and inhalation toxicity are some of the endpoints that may be evaluated [44, 45].

Drug Development and Drug Safety

Computational toxicology is applied early in the drug development process to identify potentially harmful molecules. Early forecasting can help eliminate unsuitable options before they undergo costly animal testing and human trials [46, 47].

Carcinogenicity Prediction

In silico methods can be used to identify molecular traits that are linked with cancer risk. To guess if any substance is cancerous, one can integrate QSAR models, structural alerts, and functional information. It is crucial to consider the underlying mechanisms, as carcino-genicity can involve multiple biological pathways and modes of action [48].

Mutagenicity and Genotoxicity Prediction

Many times, computer models are used to predict whether chemicals could potentially damage DNA or alter genes [49].

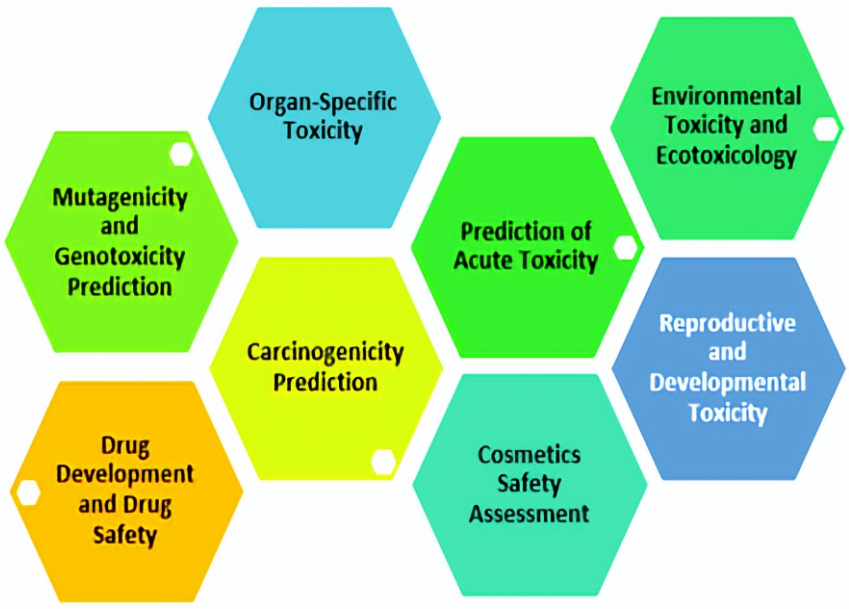


Figure 3: Showing the applications of in silico toxicity

Organ-Specific Toxicity

In silico approaches can be implemented to predict toxicity affecting specific organs. Such as the Liver (Hepatotoxicity) Kidney (Nephrotoxicity) Heart (Cardiotoxicity) Brain/nervous system (Neurotoxicity), and Lung (Pulmonary toxicity) [47, 50-51].

Reproductive and Developmental Toxicity

Computational tools can also be employed to prioritize chemicals with potential effects on reproductive system, such as fertility, reproductive organs, embryonic development and fetal development [52].

Table 1: Showing a list of some important *in silico* tools along with their key information and link where it can be accessed.

S.No.	Database	Information	Link
1.	Comparative Toxicogenomics Database (CTD) [23]	Chemical–gene–disease correlations and mechanisms of toxicity	https://ctdbase.org/search/
2.	EPA CompTox Chemicals Dashboard [24, 25]	Chemical structures, toxicity, exposure, useful for computational toxicology	https://comptox.epa.gov/dashboard/
3.	Tox21 [26]	Its Goals are **(1)** understand the mechanics of chemical -induced biological activity **(2)** prioritise compounds for more comprehensive testing **(3)** build more appropriate and predictive models of *in vivo* toxicological effects.	https://tox21.gov/
4.	Array Express / Expression Atlas [27]	Gene-expression datasets useful for toxicogenomic studies	https://www.ebi.ac.uk/biostudies/arrayexpress
5.	ToxCast [28]	High-throughput *in vitro* bioactivity and toxicity screening data for thousands of chemicals	https://www.epa.gov/comptox-tools/exploring-toxcast-data
6.	HSDB [29]	It operates through Pubchem database	https://pubchem.ncbi.nlm.nih.gov/source/11933
7.	ECOTOX Knowledgebase [30]	Toxicity of chemicals to aquatic and terrestrial organisms; useful for ecological risk assessment and QSAR	https://www.epa.gov/comptox-tools/ecotoxicology-ecotox-knowledgebase-resource-hub
8.	ProTox [31, 32]	It uses machine learning -based models to predict toxicity endpoints and toxicity targets	https://tox.charite.de/protox3/
9.	T3DB – Toxin and Toxin-Target Database [33, 34]	It contains t oxins, toxic substances, biological targets, mechanisms of action	https://www.t3db.ca/
10.	Derek Nexus v 2.0 [35]	Expert rule -based and statistic -based predictions for mutagenicity based on *in vitro* endpoints	http://www.lhasalimited.org/
11.	OECD eChemPortal [36, 37]	Provides access to chemical hazard and toxicity information from multiple international databases	https://www.echemportal.org/echemportal/
12.	EPA ToxValDB [38]	Curated toxicity values from multiple sources; useful for quantitative toxicity assessment	https://github.com/usepa/toxvaldbmain/
13.	ToxRefDB [39]	*In vivo* study data of animal toxicity for more than 1100 chemicals	https://www.epa.gov/chemical-research/downloadable-computational-toxicology-data
14.	Carcinogenic Potency Database (CPDB) [40]	Animal carcinogenicity and cancer bioassay data	https://files.toxplanet.com/cpdb/index.html
15.	TOPKAT (Accelrys discovery studio v 3.1) [41]	It predicts various range of toxicological endpoints, such as mutagenicity, developmental toxicity, rodent carcinogenicity, rat chronic lowest observed adverse effect level (LOAEL), etc.	http://www.omictools.com/toxicity-prediction-by-komputer-assisted-technology-tool

Environmental Toxicity and Ecotoxicology

In silico techniques are crucial when evaluating chemical's toxicity to environmental organisms [53].

Applications include prediction of toxicity to:

- Fish
- Algae
- Daphnia and other organisms

When appropriate experimental data is lacking or inaccessible, the OECD guidelines explicitly acknowledge the use of QSARs for aquatic toxicity prediction. In laboratory settings, QSAR techniques can be particularly beneficial [54].

Cosmetics Safety Assessment

Cosmetic safety evaluation is witnessing a rise in the use of *in silico* toxicology, especially for endpoints like sensitisation of the skin, genotoxicity, endocrine disruption, and systemic toxicity [55].

Important Regulatory Frameworks and Organizations

In silico toxicity evaluation is increasingly being integrated into regulatory toxicology as an auxiliary method for hazard detection, chemical prioritisation, data-gap resolution, and risk assessment. Numerous regulatory bodies have established frameworks, standards, and tools that facilitate the use of computational techniques including QSAR, read-across, chemical categorisation, and other predictive models.

OECD- The Organisation for Economic Co-operation and Development (OECD) (Q)SAR project has produced a number of products, including internationally recognized principles for the regulatory applications of (Q)SAR models, guidance materials and the QSAR Toolbox. The Toolbox is a software tool designed to address gaps in (eco)toxicity data required for chemical hazard assessment [48].

European Chemicals Agency (ECHA)- Within the EU chemicals regulatory system, computational tools such as QSAR and read-across may be used to improve chemical safety assessment and reduce unnecessary testing, provided there is scientific support [56].

U.S. EPA- The EPA's Safer Chemicals program develops various computational tools to help users in decision making, do research, and assess chemical information. These technologies provide a valuable resource of publicly available data related to chemistry, toxicology and exposure [25].

CDSCO- The Central drugs Standard Control Organization (CDSCO) is the National Regulatory Authority for Drug in India, and plays an important role in the regulatory assessment of novel drugs and clinical investigations. Its regulatory framework offers a platform for the incorporation of innovative non-clinical methodologies, such as computational approaches, cell-based assays, organ chips and microphysiological systems into the overall drug safety evaluation [57].

CONCLUSION

The advent of *in silico* toxicology has significantly transformed contemporary toxicology by enabling increasingly accurate predictions of chemical toxicity with little effort and expense. Techniques such as QSAR, molecular docking, read-across, machine learning, deep learning, and adverse outcome pathway analysis facilitate hazard discovery, chemical ranking and selection, drug development, risk assessment, and reduction in animal testing.

Nonetheless, effective implementation of these techniques relies on superior data quality, suitable applicability areas, thorough validation, uncertainty evaluation, transparency, and regulatory endorsement. The OECD guidelines stress the need to assess the dependability of both the model and the specific forecast prior to utilising computational outcomes for regulatory choices.

The prospects of *in silico* toxicology depend on the amalgamation of artificial intelligence with experimental and mechanistic methodologies. Instead of entirely supplanting traditional toxicology, it is probable that it will evolve into a crucial element of a comprehensive system that incorporates computational forecasts, *in vitro* assessments, omics, high-throughput screening, and focused *in vivo* investigations. This integration may expedite toxicity evaluation, enhance predictability, promote ethical considerations, and provide a more scientifically grounded approach.

FUTURE PERSPECTIVES

Moving beyond basic toxicity prediction into integrated, mechanistic, human-relevant, and data-driven safety evaluation is the way forward for *in silico* toxicology. In the coming years, we can expect increased collaboration with AI, machine learning, multi-omics, Adverse Outcome Pathways (AOPs), exposure modelling, *Systems toxicology,* digital human models, *nano-toxicology* and New Approach Methodologies (NAMs) rather than relying on independent approaches.

The notion that "computational methods replacing all laboratory testing" is a rather pessimistic view of what lies ahead. A more pragmatic and scientifically sound approach is to combine computer forecasts with in vitro data, mechanistic understanding, and carefully chosen experimental investigations. This integrated methodology has the potential to yield a more expedited, cost-effective, predictive, transparent, and ethical toxicological evaluation, thereby facilitating the development of safer medications and chemicals. The development of standardised benchmark datasets, transparent validation procedures, and interpretable AI frameworks will be crucial for broader regulatory acceptance.

Furthermore, personalised toxicology, which accounts for human genetic and metabolic variability, may enhance the accuracy of predictions regarding individual susceptibility to drugs and environmental chemicals.

CLINICAL SIGNIFICANCE

The clinical significance of this study lies in its potential to bridge the gap between research findings and practical health-care,

diagnosis, and treatment outcomes. By highlighting real-care applications. It emphasizes the importance of translating scientific observations into meaningful improvements in patient world relevance, the study contributes to evidence based medical practice and supports informed clinical decision making. Ultimately, the findings aim to enhance patient quality of life, optimize therapeutic strategies, and promote better disease management in clinical settings.

ABBREVIATIONS

QSAR: Quantitative Structure Activity Relationship
AI: Artificial Intelligence
FID: Fingerprint Identification

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AUTHOR CONTRIBUTIONS

All authors significantly contributed to the study conception and design, data acquisition, or data analysis and interpretation. They participated in drafting the manuscript or critically revising it for important intellectual content, consented to its submission to th current journal, provided final approval for the version to be published, and accepted responsibility for all aspects of the work.Additionally, all authors meet the authorship criteria outlined by the International Committee of Medical Journal Editors (ICMJE) guidelines.

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CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

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ETHICAL APPROVAL & CONSENT TO PARTICIPATE

All necessary consent & approval was obtained by authors.

CONSENT FOR PUBLICATION

All necessary consent for publication was obtained by authors.

DATA AVAILABILITY

All data generated and analyzed are included within this research article. The datasets utilized and/or analyzed in this study can be obtained from the corresponding author upon a reasonable request.

USE OF ARTIFICIAL INTELLIGENCE (AI) & LARGE LANGUAGE MODEL (LLM)

The authors confirm that no AI & LLM tools were used in the writing or editing of the manuscript, and no images were altered or manipulated using AI & LLM.

AUTHOR'S NOTE

This article serves as an important educational tool for the scientific community, offering insights that may inspire future research diretions. However, they should not be relied upon independently when making treatment decisions or developing public health policies.

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