COMPUTATIONAL TOXICOLOGY FOR DRUG SAFETY AND A SUSTAINABLE ENVIRONMENT

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Computational Toxicology for Drug Safety and a Sustainable Environment

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Computational Toxicology for Drug Safety and a Sustainable Environment

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ISBN (Online): 978-981-5196-98-6

ISBN (Print): 978-981-5196-99-3

ISBN (Paperback): 978-981-5223-00-2

First published in 2023.

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FOREWORD

It is a pleasure for me to write a foreword to the book titled, **"Computational Toxicology for Drug Safety and a Sustainable Environment"** edited by Tahmeena Khan and Saman Raza. Computational toxicology prediction is an important area to explore in present times when new chemical compounds are being developed for different applications. It is pertinent to know the fate of these chemicals on the environment for sustainable development. The book contains nine very informative chapters elaborating on different aspects and applications of computational toxicology for drug development and environmental risk assessment. The content of the book is well-written by eminent academicians and it will surely enlighten the readers to get acquainted with computational toxicology. An array of important topics like validation and sensitivity studies of computational models, computational approaches for drug profiling and development *etc.* has been included in the book. The book also reports original computational studies being done with chemical compounds to show the practical implementation of computational approaches. I recommend this book and hope it will be very useful to readers interested in toxicological studies.

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PREFACE

Toxicology is the branch of science related to the study of the toxicity of various chemicals, including their analysis and the determination of toxicity mechanisms. It finds application in various fields like food and pharmaceutical research, product development, and environmental studies. Drug toxicity is a serious issue in drug development and is the reason for almost one-third of drug attrition and late-stage failure, therefore, toxicity analysis of drug candidates at the designing stage and preclinical stage has become a must. While there are several tests and tools to detect the same, they may be costly, cumbersome, and time-consuming, consequently, computational methods and tools are being widely used nowadays to study the ADMET properties of drug candidates so that there is less financial loss and failure at a later stage. This new branch of science is called computational toxicology and it is not just being used in drug development but is also being used to study the toxicity of various chemicals that we are exposed to regularly, be it environmental pollutants, the food we eat, or the various products we use, like medicines, cosmetics, cleaning products, *etc.* Computational toxicology is a growing and multi-disciplinary research area merging diverse fields like bioinformatics and computer applications with molecular biology and chemistry.

The nine chapters included in this book explain in detail the various computational models, tools and tests that are being used nowadays for the prediction and study of the toxicity of new drug candidates as well as environmental pollutants and other harmful chemicals. The importance of computational toxicology in pharmaceutical and other industries as well as environmental studies has been elaborated on in the very first chapter. The next chapter emphasizes the importance of verification and validation of the various models that are used to assess the toxicity of substances, for more accuracy and reliability of results. One of the chapters reviews the various computational toxicological approaches for drug profiling employed for the generation of data and molecular libraries, which are highly useful in drug development. Another chapter focuses on the use of computational toxicology in environmental studies for the removal of toxins, while in another chapter, computational toxicity studies on firecrackers have been reported. In two more chapters, original research work using *in silico* studies on harmful chemicals like organochlorine compounds and drug intermediates like anisole and glyoxylic acid derivatives, have been described. The concluding chapter illustrates a more recent application of computational toxicology *i.e.*, nanotoxicology, that can be used to study the toxicity of nanoparticles and nanostructures.

This book aims to provide a comprehensive overview of the recent developments in the field of toxicology with the help of review articles and original research papers that have been authored by expert academicians and scientists. The different chapters elaborate on the strengths and weaknesses of the existing methodologies and describe the newer developments and dimensions in computational tools that can be used for greater accuracy.

The book would be useful for students pursuing post-graduation and research scholars who are pursuing a Ph.D in medicinal or environmental chemistry. Most of the books related to the topic are focused on the applications of computational strategies in medicinal chemistry, but this book is intended to explore the utility of computational strategies in medicinal as well as environmental chemistry, making it quite useful to its target readers.

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CHAPTER 1

Applications of Computational Toxicology in Pharmaceuticals, Environmental and Industrial Practices

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Abstract: Computational toxicology is a rapidly developing field that uses computational logarithms and mathematical models for a better understanding of the toxicity of compounds and test systems. This recent branch is a combination of various fields encompassing chemistry, computer science, biology, biochemistry, mathematics, and engineering. This chapter focuses on the usage of computational toxicology in various fields. This multifaceted field finds application in almost every pharmaceutical and industrial process which in turn offers safer environmental practices. Computational toxicology has revolutionized the field of drug discovery as it has helped in the production of significantly efficient drug molecules through time-saving and cost-effective methods. It has also proved a boon for various industries ranging from often-used cosmetics to daily-use food products, as toxicological assessment of chemical constituents in them provides quicker and safer production. All these computational assessments thereby save a lot of chemical wastage and thus give a helping hand in exercising healthy environmental practices. Besides this, pollutant categorization and waste management through computational tools have also been favoured by many agencies that work for environmental sustainability. Thus, to sum up, computational technology has completely transformed the processes and practices followed in pharmaceutics, environment protection and industries, and paved the way for efficient, cost-effective, and less hazardous routes.

Keywords: Computational toxicology, Drug discovery, Environment, Industry, Pharmaceutics.

INTRODUCTION

Computational toxicology is a rapidly advancing technology that uses mathematical models designed from integrated data, through easy computer-based

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software applications or programs, for the prediction of metabolic and toxic properties of chemicals, drugs, edible items, pollutants and others [1]. This prediction can help reduce the synthesis time as well as the efficiency of many products without any detrimental effects to the environment. The branch of computational toxicology integrates various disciplines in it like chemistry, mathematics, biochemistry, medicine, computer science, biology and engineering [2, 3]. An integrated approach to various scientific fields in computational toxicology is depicted in Fig. (**1**). Besides toxicological predictions, it also predicts metabolic interaction predictions of chemicals at cellular and molecular levels in biological systems, thus making it a useful branch of study in multifarious fields [4]. The integrative approaches for toxicological research are modelled into computational tools for easy usage by researchers and scientists [5]. This predictive modelling assessment has greatly reduced the time consumed in the production of drugs, cosmetics, and food products, the unnecessary hazardous effects of chemical wastage on the environment, and the usage of *in vivo* methods and reliance on animal testing, and has improved the efficacy of drugs and cosmetic products with minimum health hazard risks [6].

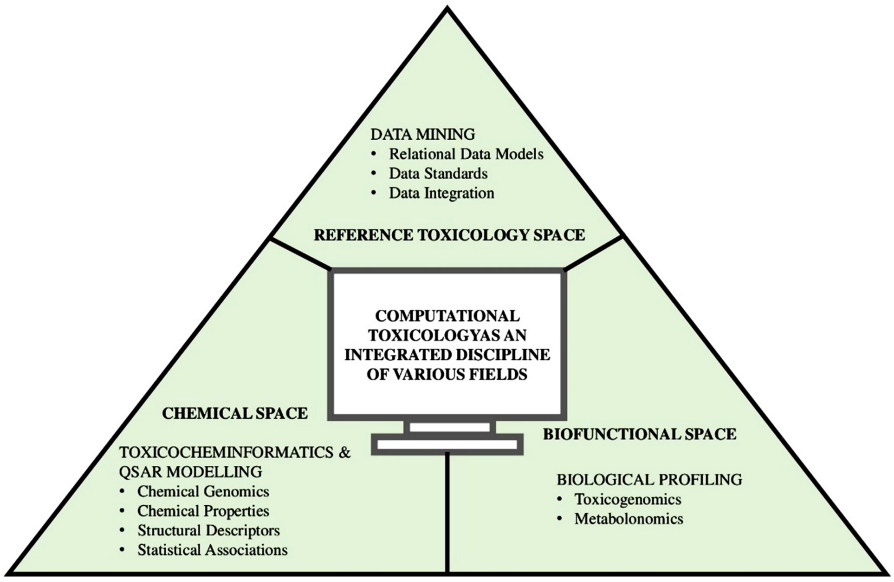

Fig. (1). Computational toxicology as an integrated sub-discipline of various disciplines.

The integrated computational models for toxicological assessment are prepared through sequential steps. The general steps involved in the preparation of each model include a series of steps starting from the identification of user needs, followed by data collection, further followed by its expert assessment and data

cleanup, succeeded by data harmonization or data standardization and finally ending at toxicity assessment [7, 8]. These basic steps form the basis of each artificial intelligence-based predictive model in computational toxicology. The first step ensures that the demand of the user is met *i.e*., a clear picture of user needs is required to be known; For example, if it's toxicity assessment of some hazardous pollutant, data collection should be according to it, or if it is an assessment for toxicity of any chemical compound or permissible limits of any component in products, then the data must be collected accordingly as per those needs or if the manufacturer tends to prepare a new formulation, then the data for comparative toxicological limits of various chemical components must be curated [9, 10]. A clear start gives the best ending for our prediction models. Thus, the identification of appropriate users' needs helps in identifying the regulatory endpoints for predictive assessment [11]. The second step includes data collection which is as per the requirements of the user. Sufficient metadata and reproducible data are the key points for the development of a reliable model. Data are collected from primary data reports, aggregated reports, repositories like PubChem, or through already existing computational predictive models.

The third step takes into account expert assessment which involves the evaluation of data by subject matter experts for additional contexts to existing or incomplete data or the removal of irrelevant data. The fourth step involves data cleanup where erroneous data is identified and sorted out for better and more efficient assessment [12 - 14]. This step addresses any changes in spelling, special characters, and typographical errors incompatible with the computational tools and resolves these inconsistencies through automated workflow processing of data. The next step includes data harmonization or standardization where the sorted data is standardized for being compatible with the integrated chemical environment, to increase its interoperability like with EPA CompTox chemicals dashboard. In this step, data is standardized as per authoritative and regulatory standards [15, 16]. The final step uses the standardized data in conjunction with an integrated chemical environment or other descriptors for toxicity assessment. These sequential steps are diagrammatically explained in Fig. (**2**).

Computational toxicology has numerous advantages over traditional toxicology testing methods. It is a timesaving, cost-effective, eco-friendly approach as compared to the *in vivo* approach where actual animal models are used for toxicity prediction studies causing loss of lives as well as chemicals and time. These *in silico* or *in vitro* models are accurate as well as advantageous in terms of time and economic and ecological practices. Thus, computational toxicology is highly advantageous over traditional toxicology testing.

CHAPTER 2

Verification, Validation and Sensitivity Studies of Computational Models used in Toxicology Assessment

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Abstract: Complex computational models of biological systems are developed to simulate and emulate various biological systems, but many times, these models are subjected to doubt due to inconsistent model verification and validation. The verification and validation of a model are important aspects of model construction. Moreover, the techniques used to perform the verification and validation are also important as the improper selection of the verification and validation techniques can lead to false conclusions with profound negative effects, especially when the model is applied in healthcare. The objective of this chapter is to discuss the current verification and validation techniques used in the analysis and interpretation of biological models. This chapter aims to increase the efficiency and the peer acceptability of the biological prediction models by encouraging researchers to adopt verification and validation processes during biological model construction.

Keywords: Model validation, Prediction model assessment, Toxicology assessment, Toxicology, Verification.

INTRODUCTION

Modelling is an emerging technique in the field of biology to make experiments and product designs more efficient. Simulation and modelling of humans and the environment play a major role in propelling biological and clinical research by helping understand their mechanistic and systematic properties in detail [1, 2].

With the increased use of *in silico* clinical trials for the development and validation of novel drugs, the credibility of these modelling has gone beyond academia, with regulatory agencies and industry exploiting them for virtual testing of pharmacological therapies [3 - 6].

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Not just in clinical trials, but these techniques are also helping to reduce and replace animal experimentations and bench tests [7 - 10].

As the *in silico* results are also been increasingly included in the regulatory filings, the regulatory authority and the research community should incorporate a level of minimum requirement for scrutiny of the reported *in silico* results in both research publications and regulatory submissions. Given this, various model credibility evaluation processes have been introduced including the ASME VV-40-2018 standard along with a recent guideline for the PBPK simulation modelling reports by the EMA [11].

The acceptance of predictive models in toxicology is slow because regulators do not confidently believe in a new approach. So, several validation frameworks have been formed [12]. These include internationally recognised rules on validation by the JRCs.

European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) is a highly curated knowledge base [13, 14]. Initially, the emphasis was on *in vitro* methods but subsequently re-interpreted and adapted for computational methods including assessment frameworks for quantitative structure-activity relationships (QSARs), and the physiologically based kinetic (PBK) models [15, 16].

Over the recent years, it has been seen that the difference between *in vitro*/*in vivo* and *in silico* techniques in toxicology has been blurred. The experiments are relying largely on sophisticated complex computational approaches to analyse the data they generate and the mathematical and machine learning models generated by the computational methods are dependent on the experimental data for parameterisation and validation. Owing to this blurred distinction, frameworks for data assessment, integration, characterization, and weight of evidence have been developed by the regulatory authorities [17]. The generic assessment framework is shown in Fig. (**1**).

Verification is defined as the process of determining that the proposed mathematical model is accurately represented by the constructed computational model. Validation is defined as the process of determining the accuracy of the model in the real world from the perspective of the context of usage. In general, validation must succeed verification to check for errors in model implementation from uncertainties during model formulation [18 - 20]. The workflow of the verification and validation of a mathematical model is shown in Fig. (**2**).

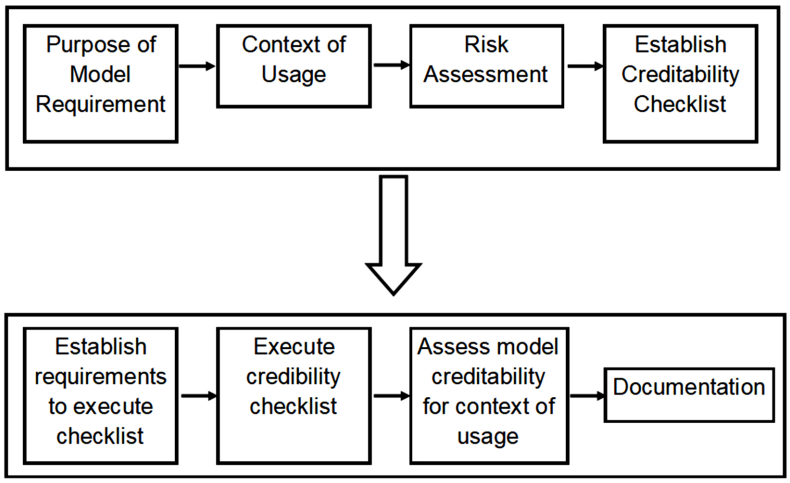

Fig. (1). The generic workflow of the credibility assessment framework.

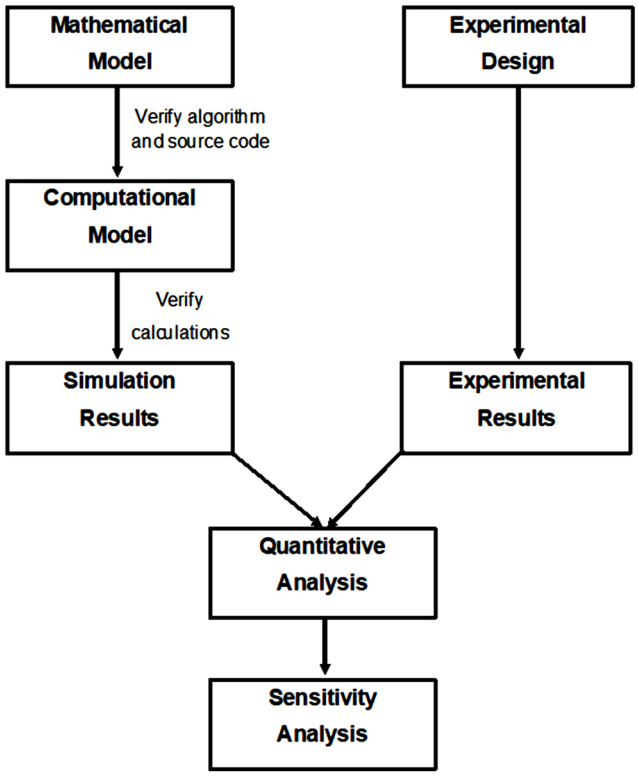

Fig. (2). The workflow of the verification and validation of a mathematical model.

CHAPTER 3

Computational Toxicological Approaches for Drug Profiling and Development of Online Clinical Repositories

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Abstract: One of the chief reasons for drug attrition and failure to become a marketed drug is the potential toxicity associated with its administration. Therefore, many drugs encountered in the past reached the last phase of drug development successfully but could not be marketed despite their potential drug-likeness due to their inevitable toxicity properties. This issue can be addressed considerably by employing computational toxicological approaches for predicting the toxicity parameters of a drug candidate before its practical synthesis. Pharmaceutical companies utilise computer-based toxicity predictions at the design stage for identifying lead compounds possessing the least toxic properties, and also at the optimization stage for selecting candidates as potential drugs. This integrative field has been exploited for various applications including hazard and risk prioritization of chemicals and safety screening of drug metabolites. The importance of QSTR models for the computational prediction of toxicity is also discussed in this chapter. Various important and predominant software for *in silico* toxicity prediction including ADMETox, OSIRIS Property Explorer, TopKat and admetSAR 2.0 are also covered herein. This chapter also discusses various freely accessible online clinical repositories such as BindingDB, PubChem, ChEMBL, DrugBank and ChemNavigator iResearch Library. Therefore, the present chapter focuses on the role played by computational toxicology in the procedure of drug profiling and in establishing freely accessible online clinical repositories.

Keywords: SARS-CoV-2, SARS, Nucleocapsid protein, Spike protein, Envelope protein, NAAT, OTC tests, RT-PCR, Gag-Pol polyprotein, RdRp, MERS, ACE-2.

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INTRODUCTION

Computational toxicology is an ever-evolving technique involving collecting and amalgamating data from diverse sources to obtain *in silico* mathematical models. This subdiscipline of toxicology facilitates an in-depth understanding and prediction of hazardous health impacts associated with various environmental pollutants and pharmaceuticals [1]. It utilizes mathematical and statistical modelling and computational tools to comprehend the mechanisms of action of a chemical that causes adverse effects in an organism or environment [2]. Fig. (**1**) shows an outline of the role of machine learning (ML) and computational tools in drug development and toxicity prediction.

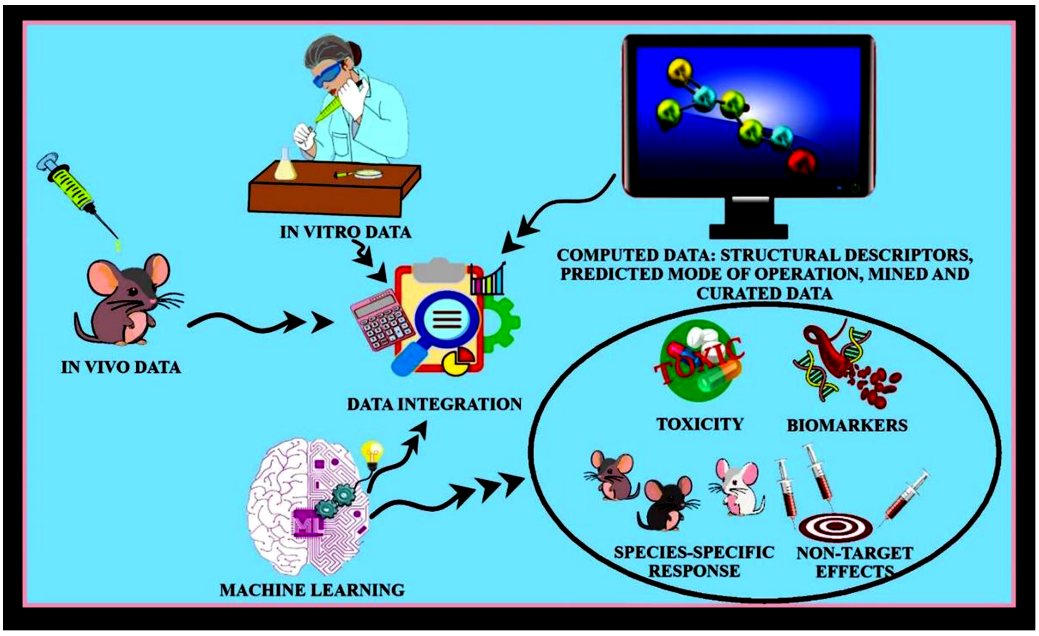

Fig. (1). An outline of the role of machine learning and computational tools in drug development and toxicity prediction.

Pharmaceutical companies employ computer-based toxicity predictions at the design stage for identifying lead compounds possessing the least toxic properties, and the optimization stage for selecting candidates as potential drugs [3]. The capability of *in silico* approaches for predicting the ADMET (Adsorption, Distribution, Metabolism, Excretion and Toxicity) parameters of virtual molecular structures permits the investigation of the chemical space before their chemical syntheses and experimental tests. Determining the toxicity of chemicals is imperative for drawing information about their detrimental effects on living organisms and the environment. It is a dependable alternative for animal models

that are conventionally used. The animal models are economically challenging and require an ample amount of time. Computational toxicology methods have been utilized in drug discovery in the early 2000s aimed to predict properties such as DILI (drug-induced liver injury), hERG inhibition (human ether-a-go-go-related gene) [4], bacterial mutagenicity, *etc.* [5]. Since then, it has been continually developing with enhanced methodologies and increased complexities. This field holds prime importance as it assesses drug safety and associated risks, complementing both *in vitro* and *in vivo* methods. It is inevitable to use computational toxicology in almost every phase of drug discovery and development. Its applications range from profiling enormous libraries (at the initial stage) and predicting off-target effects (mid-discovery phase) to evaluating probable mutagenic impurities in development and degradants as part of life-cycle management [6]. Safety issues are a significant attrition for drug candidates' failure in the present time [7]. Considerable computational approaches exist to predict the toxicity induced by a small molecule by using its chemical graphic [8]. Traditionally, it finds applications in predicting global toxicity endpoints *viz.*, carcinogenicity, mutagenicity, *etc.* [9, 10]. This integrative field has been exploited for various applications including hazard and risk prioritization of chemicals and safety screening of drug metabolites. The present chapter focuses on the role played by computational toxicology in the procedure of drug profiling and in establishing freely accessible online clinical repositories. The importance of computational toxicology for drug discovery and development and regulatory decisions in public health has been highlighted herein [2].

DRUG TOXICOLOGY

Drug toxicology includes both toxicokinetic parameters as well as toxicodynamic parameters. Toxicokinetics (a toxicological equivalent of pharmacokinetics) encompasses the movement of toxicants into the body while toxicodynamics (a toxicological equivalent of pharmacodynamics) deals with responses to a compound when exposed to cells or in other words the interaction of toxicants with the cell receptors *i.e.* the formation of the toxicant-receptor complex. when exposed to different organs/tissues in the body. The toxicokinetics-toxicodynamics correlation suggests an association between the concentration of toxicants in blood and the responses after rigorous analysis of results concerning ADMET parameters [11]. Fig. (**2**) shows the two key concepts of drug toxicology.

DRUG PROFILING

Drug profiling is a method that aims to extract information related to a drug sample and predicts the probable synthetic procedure or precursor for it. Once a target is identified, the various effects of the drug can be measured. The formation

CHAPTER 4

How to Neutralize Chemicals that Kill the Environment and Humans: An Application of Computational Toxicology

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Abstract: Computational toxicology is an applied science that combines the use of the most recent developments in biology, chemistry, computer technology, and mathematics. Integrating all of these fields into a biologically based computer model to better understand and anticipate the negative health impacts of substances like environmental contaminants and medications. As public demand rises to eliminate animal testing while maintaining public safety from chemical exposure, computational approaches have the potential of being both rapid and inexpensive to operate, with the ability to process thousands of chemical structures in a short amount of time. The agency's computational toxicology lab is always working on new models for decision-support tools such as physiologically based pharmacokinetic (PBPK) models, benchmark dose (BMD) models, computational fluid dynamics (CFD) models, and quantitative structure-activity relationship (QSAR) models. The models are being used to analyze the toxicological effects of chemicals on mammals and the environment in a variety of industries, including cosmetics, foods, industrial chemicals, and medicines. Additionally, the toolbox's understanding of toxicity pathways will be immediately applicable to the study of biological responses at a variety of dosage levels, including those more likely to be typical of human exposures. The uses of computational toxicology in environmental, pharmacological, and industrial processes are covered in this study.

Keywords: Computational toxicology, Environment, Human, *In silico* models.

INTRODUCTION

The goal of toxicity testing is to determine whether a drug has negative effects on people, animals, plants, or the environment after a single or repeated exposure. How dangerous a substance is, depends on its chemical, biological, and ADME properties as well as the route of administration, dose, frequency, and length of exposure [1].

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Animal testing has historically been used extensively in the assessment of chemical hazards and risks. In addition to having a limited ability to anticipate the consequences on human and environmental health, these studies can be expensive, time-consuming, and unethical. Additionally, it is impractical to use animal testing to assess the health risks of the tens of thousands of different chemicals that are already on the market but lack toxicological information [2]. Before introducing any new chemicals or pharmaceuticals into use in industry or commerce, it is important to first investigate how harmful they are to ecosystems and living beings. Toxic chemicals cause environmental concerns, and the majority of these problems are caused by complex chemical formulations [3]. When new compounds are introduced, the majority of companies only offer data on one chemical's toxicity. As a result, information on the toxicity of multi-chemical mixtures is uncommon and even more intriguingly, mixtures may exhibit various toxicity responses depending on the chemical ratio [4]. Chemicals' effects eventually result from their direct or indirect molecular interactions with one or more biological components. These interactions can involve the binding of a receptor or an enzyme, lipid membrane rupture, localized generation of free radicals, or non-specific dephosphorylation. However, if two substances have comparable biological interactions, the same distribution, and kinetics inside an organism, then the two substances should exhibit comparable bioactivity profiles and potentially harmful effects [5]. Numerous studies published over the past few decades have demonstrated that a variety of exogenous chemicals can affect hormone levels or hormone activity, leading to hazardous effects. Endocrine-disrupting chemicals (EDCs) have been identified as a new class of dangerous substances as a result, and their mechanisms of action will be used to identify them rather than their chemical makeup or intended use at first. Exogenous hormone-disrupting compounds, or EDCs, cause a variety of metabolic, immunological, neurological, reproductive, and developmental disorders in both people and wildlife [6].

The ability to predict the toxicological side effects of new chemical entities is critical to improving the efficiency of costly drug discovery. In most of the countries where animal experimentation is restricted, there has been growing concern over the use of animals for *in vivo* chemical testing, which has led to the emergence of legislation [7]. *In silico* toxicology, also known as computational toxicology, is a branch of toxicity assessment that collects, analyses, models, simulates, visualizes, or predicts the toxicity of substances using computational resources (methods, algorithms, software, data, *etc.*) [8]. It is linked to *in silico* pharmacology, which analyzes the therapeutic beneficial or adverse effects of medications using data from computational tools [9]. Many predictive tools used in the current safety paradigms were designed to recognize risky compounds early in the drug discovery process, enabling a ‘fail early’ strategy [10]. Computational

toxicology relies on knowledge from several scientific domains, and it works under the assumption that a chemical's toxicity may be predicted from its molecular structure and inferred from its features [11]. This assertion is true for the development of (Q)SAR models as well as for the calculation of risk assessment utilizing expert guidelines, which allow the identification of dangerous compounds based on so-called warnings, and straightforward structural elements linked to the manifestation of toxicity [12].

Robust and accurate models for toxicological endpoints may be developed and validated owing to the tremendous development of data from biology, physics, and chemistry. The advancement of better computer science tools for modelling and chemical manipulation has kept pace with the increase of the data. The capability of computational models for toxicology has increased as a result of the availability of chemical data and the wide range of modelling tools [13]. There are several different computational tools used in *in silico* toxicology such as databases for gathering data on drugs' toxicity and other chemical characteristics; molecular descriptor generation software.; molecular dynamics and systems biology simulation software; modelling tools for toxicity prediction; statistical software and modelling tools for building prediction models; Web servers or standalone apps that use expert systems with built-in models to forecast toxicity; and tools for visualizing [1]. The present study comprises a wide range of topics, including quantitative structure-activity relationships (QSAR), artificial intelligence (AI) and machine learning (ML), and other *in silico* studies.

MAJOR CATEGORIES FOR *IN SILICO* TOXICOLOGY TOOLS

There are several methods to determine the toxicity or safety of a general or specific substance, and each one has unique advantages, disadvantages, applications, and interpretations. *In silico* tools may be broadly categorized into four main groups namely Cheminformatics, Structure-activity modelling, Data sources, and Data analysis and mining (Fig. **1**), each of which differs in complexity and performance [14].

TOOLS AND DATABASES FOR TOXICITY PREDICTION

Research advances in the field of drug development heavily rely on *in silico* methodologies and techniques that make use of experimental data to enable precise property/activity assessment using several computer tools. It is highly recommended to avoid using animal testing, when possible, especially when performing toxicity and risk assessments, as *in silico* technologies can considerably cut down on the amount of time and money spent on experimental procedures. Databases are the source from where one can retrieve the chemicals/compounds/molecules of interest and to date, there are many databases

CHAPTER 5

Adverse Environmental Impact of Pharmaceutical Waste and its Computational Assessment

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Abstract: Pharmaceuticals are necessary products that have indubitable benefits for people's health and way of life. Following their use, there is a corresponding increase in the production of pharmaceutical waste. We need to figure out how to lessen the production of pharmaceutical waste and prevent its release into the environment, which could eventually pose major health risks to the rest of the living world. If handled incorrectly, pharmaceutical waste increases the danger, which is inversely correlated with the active concentration of chemical components in various environmental compartments. As a result, when drugs and their unaltered metabolites are dispersed into the environment through several sources and channels, they may influence both animals and humans. Finding the sources and points of entry of pharmaceutical waste into the ecosystem is the first step in understanding pharmaceutical ecotoxicity. Several techniques, like the Structure-Activity Relationship (SAR) and Quantitative Structure-Activity Relationship (QSAR) models, help assess and manage environmental risks caused by pharmaceutical waste. The persistency, mobility, and toxicity (PMT) of pharmaceutical compounds have been predicted computationally using QSAR models from OPERA QSAR, VEGA QSAR, the EPI Suite, the ECOSAR, and the QSAR toolbox. *In silico* predictions have been made for molecular weight, STP total removal, sewage treatment plant, Octanol-water partition coefficient (KOW), ready biodegradability, soil organic adsorption coefficient, short- and long-term ecological assessments, carcinogenicity, mutagenicity, estrogen receptor binding, and Cramer decision tree. The adverse effects of medications on the living world, as well as risk assessment and management, have been covered in this chapter. Several computational methods that are employed to counteract the negative consequences of pharmaceutical waste have also been addressed. The goal is to better understand how to minimize the concentration of pharmaceutical waste in our environment.

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Keywords: Biodegradability, Computational, Environment, Pharmaceutical waste, Risk assessment, QSAR.

INTRODUCTION

Pharmaceuticals are one essential good with undeniable advantages for people's health and way of life. Drug development, an ageing population in Western nations, and initiatives to improve health in developing nations are all driving factors in the widespread distribution of medicines and the steady global rise in the use of potent pharmaceuticals. The majority of people around the globe will take more than one dosage of medication each day. This usage is followed by a commensurate rise in the production of pharmaceutical waste. It is crucial to reduce waste production and the chance that waste will release hazardous pharmaceutical compounds into the environment [1]. Since 1970, active pharmaceutical ingredients (APIs) have unfortunately been detected in several environmental compartments due to misuse and poor disposal of medications [2]. Pharmaceuticals are specifically created to have an impact on particular organs, tissues, or cells in living systems and many of them remain persistent in the body. This is known as having an explicit mechanism of action (MOA) [3]. This prompts questions regarding the contamination's possible negative effects on the ecosystem. Pharmaceutical waste, if improperly managed, raises the risk which is directly proportional to the active concentration of the chemical compounds in various environmental compartments. As a result, when medications and their unmodified metabolites are released into the environment through a variety of sources and channels, they can have an impact on both animals and humans [4].

Pharmaceuticals are a class of compounds with significant social importance as healthcare aids. In surface, ground, and drinking waters, a range of medications have been found. Concerns are raised regarding the contamination's possible negative effects on the ecosystem. If pharmaceutical waste is not managed appropriately, it increases the risk which is directly proportional to the active concentration of the chemical compounds in various environmental compartments [5]. It is abundantly evident that the toxicity of medications on organisms in aquatic and nonaquatic environments is caused by their long-lasting and bioaccumulative nature [6]. In the environment, particularly in surface water and sewage effluent as well as in groundwater and soil samples for more than 71 nations worldwide, almost 600 APIs or their metabolites and transformation products have been discovered. In aquatic and terrestrial compartments, more than 200 APIs from medicinal groups of analgesics, antihypertensives, antibiotics, and antidepressants have been found [7, 8]. The majority of APIs are partially degraded or handled at wastewater treatment facilities (WWTPs) and then released into the aquatic environment, causing continuous and widespread

pollution [9]. Unsafe disposal methods and the excretion of toxins through faeces and urines into the sewage system result in a significant amount of contaminants being released. Hospitals and industries, whose effluents are laden with very high concentrations of APIs and their metabolites, are additional substantial sources of pharmaceuticals [10]. Active pharmaceutical ingredients (APIs) are becoming increasingly popular across the world. As a result, these compounds have emerged as contaminants of emerging concern (CEC), posing risks and toxicity to aquatic and terrestrial life systems, as well as people. Regulatory bodies from all around the world have developed a plethora of rules, standards, and laws for assessing the danger of drugs to the ecosystem. Because generating a large amount of experimental data is time-consuming and expensive, as well as requiring the sacrifice of a large number of animals, computational modelling or *in silico* approaches are proving to be an efficient technique for not only risk assessment but also risk management and data gap filling [11].

SOURCES

To comprehend pharmaceutical ecotoxicity, the first step is to identify their origins and entrance points into the ecosystem. The major origins and well-known channels for pharmaceutical contamination in the environment are depicted in Fig. (**1**).

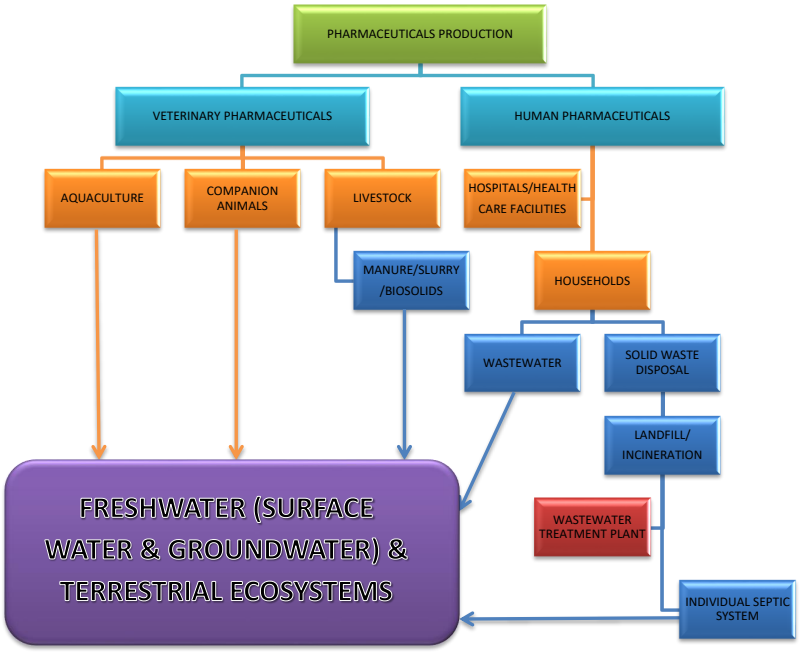

Fig. (1). Different sources of pharmaceutical waste.

CHAPTER 6

Computational Aspects of Organochlorine Compounds: DFT Study and Molecular Docking Calculations

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Abstract: The paper and pulp industry generates enormous amounts of wastewater containing high quantities of chlorinated toxicants. These volatile organochlorine compounds are widespread toxic chemicals that may cause harmful effects on humans *via* interaction with human α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (hACMSD) which is a vital enzyme of the kynurenine pathway in tryptophan metabolism. It averts the accumulation of quinolinic acid (QA) and supports the maintenance of the basal Trp-niacin ratio. Herein, we report the optimization of organochlorine compounds employing density functional theory (DFT) with B3LYP/6-311G+(d,p) basis set to elucidate their frontier molecular orbitals as well as the chemical reactivity descriptors. The DFT outcome revealed that organochlorine compounds show a lower HOMO-LUMO gap as well as a higher electrophilicity index and basicity as compared to the substrate analogue, Dipicolinic acid. To assess the structure-based inhibitory action of organochlorine compounds, these were docked into the active site cavity of hACMSD. The docking simulation studies predicted that organochlorine compounds require lower binding energy (-3.86 to -6.42 kcal/mol) which is in good agreement with the DFT calculations and might serve as potent inhibitors to hACMSD comparable with its substrate analogue, Dipicolinic acid which has a binding affinity of -4.41 kcal/mol. Organochlorine compounds interact with key residues such as Arg47 and Trp191 and lie within the active site of hACMSD. The high binding affinity of organochlorine compounds was attributed to the presence of several chlorine atoms, important for hydrophobic interactions between the organochlorine compounds and the critical amino acid residues of the receptor (hACMSD). The results emphasized that organochlorine compounds can structurally mimic the binding pattern of Dipicolinic acid to hACMSD.

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Keywords: Basis set, Binding affinity, Descriptors, DFT calculations, Dipicolinic acid, Docking, Frontier molecular orbitals, hACMSD, HOMO-LUMO gap, Inhibitors, Kynurenine, Organochlorine compounds, Quinolinic acid, Receptor.

INTRODUCTION

Environmental pollutants resulting from large-scale industrial wood processing represent a serious global challenge to sustainable development. Removal of process contaminants from pulp and paper production has increased significantly in recent years, but these industries still generate large-scale wastewater containing large amounts of chlorinated pollutants [1]. Large amounts of wastewater and the release of significant amounts of potentially harmful compounds are formed during several different stages of the papermaking process, including pulping, bleaching and washing [2]. Pulp and paper production is trying to make the transition to become more sustainable, and has both elemental and total chlorine-free paper processes that greatly reduce the presence of harmful substances i.e., considered toxic in some countries [3]. However, conventional chemical grinding and bleaching operations based on the sequential addition of chlorine, hypochlorite and chlorine dioxide, together with the use of acidic sulphur dioxide bleach and the addition of sodium dithionite, are still used widely to obtain white and glossy paper products [4]. These treatment steps result in the release of many free constitutive chlorine compounds, some of which are resistant to spontaneous decomposition. Consequently, wastewater produced from major pulp and paper processing operations is now characterized by containing many problematic substances, namely chlorophenols, sulfonated lignin flakes, a wide range of sulphur by-products, various resins, as well as various products with high biological oxygen demand and inorganic salt concentration [5]. Wastewater is potentially toxic and dangerous to the environment. In addition, the toxic effects of some of these compounds on human health are significant and include mutagenic and possibly endocrine-disrupting effects [6]. As mentioned above, pulping and bleaching are the main steps in which various toxic pollutants are formed, *i.e.* volatile organochlorine compounds [7]. In particular, the pulp and paper industry generates large amounts of wastewater containing large amounts of organochlorine compounds. The presence of these compounds in wastewater is a serious environmental and toxic problem. Organochlorine toxins are harmful to the environment and human health because they have carcinogenic, mutagenic, cytotoxic and endocrine-disrupting effects. To address these most pressing concerns, the use of the human enzyme α-amino-β-carboxymucona-e-ε-semialdehyde decarboxylase (hACMSD) for toxicity studies was developed. Several studies have reported that ACMSD is an important enzyme for tryptophan metabolism [8].

In the brain, elevated quinolinic acid (AQ) levels are often implicated in the pathogenesis of various neurodegenerative disorders, including Alzheimer's disease and Huntington's disease [9]. In the tryptophan metabolism of kynurenine, α-amino-β-carboxymuconate-ε-semialdehyde (ACMS) is converted into α-amin--β-muconate-ε-semialdehyde (AMS) through the action of the important enzyme ACMS decarboxylase, AMS is then converted into acetyl CoA [10]. To maintain the basal Trp-niacin ratio, ACMS is not enzymatically converted into quinolate (QA), which further leads to the formation of NAD [11]. Therefore, the presence of the key enzyme ACMSD prevents quinolate accumulation [12]. Disruptions in basal AQ levels have been implicated in many physiological and pathological conditions involving the central nervous system (CNS) [13]. Thus, ACMSD acts as a checkpoint and regulates the balance between relative AQ levels. In this study, we explore organochlorine pollutants generated during pulp and paper processing, summarized the toxicological effects of these compounds, and highlighted their ability to inhibit enzymes α-amino-β-carboxymucona-e-ε-semialdehyde decarboxylase (hACMSD) in humans. We highlight computational methods, including density functional theory (DFT) and molecular docking that are currently giving momentum to the toxicity study of pollutants.

Organochlorine compounds have been shown to increase AQ production in rats [14]. This study revealed that the structural similarity of organochlorine with tryptophan metabolites was responsible for the remarkable changes in normal tryptophan metabolism and caused the inhibition of ACMSD activity. Although many studies have shown that organochlorine is involved in the breakdown of the basal trp to niacin ratio, elucidation of the important mode of binding and interaction of organochlorine with hACMSD has not yet been achieved. This study highlights the important interactions of organochlorine compounds with human α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (hACMSD) that can inhibit hACMSD activity and lead to the accumulation of quinolate. Crystal structures of hACMSD, as well as substrate-like dipicolinic acid (PDB ID: 4IH3), are available [15]. Dipicolinic acid binds to the zinc-containing active site of hACMSD and shows an interaction with Arg47 and Trp191. In this study, the most common organochlorine compounds produced by the pulp and paper industry that were used for hACMSD binding studies were: 4-chloro-2-methoxyphenol, 5-chlorovanillin, 2,3,7,8-tetrachlorodibenzo-p-dioxin, 4,5-dicloguaiacol, 4-clocatechol, 2,3′,4,4′,5-pentachlorobiphenyl, 2,3,6,7-tetr--clonaphthalene, 4-chlorine -3-Metylphenol, 2-Clophenol, 2, 4,6-Trichlorophenol, Pentachlorophenol, 4,5-Dichlorocatechol, 6-Clorovanillin, 3,4-Dichlorophenol. Molecular docking studies were used to investigate the binding mode and stability of these organochlorine compounds to human ACMSD. The results concluded that these organochlorine compounds could effectively bind and inhibit hACMSD activity. Thus, the binding of organochlorine to hACMSD affects the ratio of trp

CHAPTER 7

Toxicology Studies of Anisole and Glyoxylic Acid Derivatives by Computational Methods

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Abstract: Toxicology is a domain imbricating biology, chemistry, pharmacology, and medicine that involves observing and analyzing inauspicious consequences of chemical exposure on living beings thus identifying and manifesting toxins and toxicants. Progress in computer sciences and hardware in combination with equally remarkable growth in molecular biology and chemistry are providing toxicology with a reigning new tool case. This tool case of computational models assures to enhance the efficacy by which the hazards and risks of environmental chemicals are driven. In this study, we investigated two compounds namely: Phenylgloxylic acid (PGA) and 4-ethynyl anisole (MOPA) experimentally as well as quantum chemically. Density functional theory was employed to investigate the tilted compounds theoretically. All the Quantum chemical calculations were performed by implying the Density functional theory technique, B3LYP method and 6-311++G (d, p) basis set. The reactive areas of the molecule were obtained by Fukui functions. The ADME properties and drug-likeness nature of the derivatives were obtained by SwissADME Tool [1]. Molecular docking studies were also performed with different receptor proteins to study the best ligand-protein interactions. The biological study-drug-likeness was also performed to check the drug-like nature of the molecule.

Keywords: ADME, AutoDock, Bayesian, B3LYP method, Computational toxicology, Chimera, DFT, Drug, Drug-likeness, Docking, Electrophilicity index, Fukui, Machine learning, Orca, 6-311++G (d, p) basis set.

INTRODUCTION

Computational toxicology examines the stimulus and response of chemical agents on live forms across demography and individuals on a cellular and molecular level.

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Applications of this multi-specialized field range from hazardous and risk prioritization of chemicals to safely screening drug metabolites, having active recognition and growth from many organizations that include government sectors, non-profit organizations, private sectors, and research and development department. Our focus is to embrace new approaches to drug discovery. The ongoing way is to make simpler predictions, to demonstrate the additional prognostic power derived from these tools. The *in-silico* drug discovery or techniques enable the reduction of the cost incurred by predicting adverse drug reactions or drug-target interaction in preclinical studies.

The goal of computational chemistry is to provide a concrete and scientific elucidation of a drug beforehand to enable the industry to have a cost-effective measure in the drug manufacturing process. Computational chemistry is an accurate tool for determining the properties of isolated molecules within the framework of quantum mechanics. The following step starts from isolated molecules or atoms to a more complex potential system that is still under evolution. There are many approaches in use. Computational models are widely applicable to toxicology across pharmaceutical, environmental fields, and end-consumer products over the past decades. The increasing raw data for defined toxicology endpoints have provided us with a larger sample size for machine learning models for accurate predictions.

Bayesian and SVM models operate on the principle of cross-validation data. Huge advancement has been made in computational toxicology in a decade in both model development and the availability of precise and accurate large-scale data models. Advanced research in toxicology data generation will result in compounds that are readily accessible for machine-learning models on an industrial scale.

For quantized chemical calculations in molecules, Density functional theory (DFT) is a suggested study for a better depiction of polar bonds. All calculations were based on 6-311++G (d, p) higher order basis set and B3LYP method. The calculations in the present work were carried out using the Gaussian 03W program package in individual capacity and fine results were obtained by ORCA 4.0.1. By optimizing the geometry of the molecule using the B3LYP method with 6-311++G (d, p) as the higher basis set the geometrical parameters and vibrational wavenumbers were computed. Vibrational tasks were performed by the VEDA4 software in the semblance of potential energy distribution. The vibrational wavenumbers, geometrical parameters and other molecular properties like HOMO-LUMO were accomplished by the optimized structure. ADME properties and the drug-likeness nature of the target molecules are procured using SwissADME Tool. The listed graphs were extracted using Multiwfn software or

Origin8.0 software. The goal is to show how these models are used in industries and academia and their effect as well as suggestions for the future.

SOFTAWARES

Gaussian Program

Gaussian program is general software, discovered in 1970 by John Pople [1 - 5] and his research group at Carnegie Mellon University as Gaussian 70. This software constantly updated since Gaussian 09. There are two Gaussian programs interlinked- Gaussian and Gauss view.

Gaussian program is used for calculation whereas, the Gauss view is for visualization in computational chemistry for the different properties of molecules such as molecular energies, structure, transition state energies, vibrational frequencies, IR and Raman spectra, reaction pathway, atomic charges, dipole moment, NMR shielding and magnetic susceptibilities, polarizabilities and hyperpolarizability, electron densities and electrostatic potential. Gaussian functions are used to blur/smooth images. Mathematically, Gaussian functions are derived as Equation **1**:

$$(x) = \quad \alpha e^{-(x-b)^2/2c^2} \qquad \textbf{(1)}$$

Where α, b and c are arbitrary real constants. "Bell curve" is observed from Gaussian where 'α' represents the height of the curve apotheosis, 'b' represents the position of the apex of the curve and 'c' represents the standard deviation in the curve. The Gaussian function used in spatial filtering is known as Gaussian filtering [6].

Some applications of the Gaussian program are as follows:

• A Gaussian function is the wave function of the ground state of the quantum harmonic oscillator.

• Linear combination of molecular orbitals in computational chemistry is called Gaussian orbitals.

• Hermite functions are used to derive the Gaussian function mathematically.

• In Geostatistics, they are used for understanding the variability between the patterns of a complex training image. They are used with kernel methods to cluster the patterns in the feature space [7].

CHAPTER 8

Computational Toxicology Studies of Chemical Compounds Released from Firecrackers

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Abstract: Customary firework burning during different festivals and occasions have been reported from different parts of the world. The pollutants emitted from fireworks exert toxicological effects on human health and the environment. A virtual study was performed to assess the extent of binding of sixteen important components of fireworks including Al_2O_3, $Ba(NO_3)_2$, C_6H_6, CO, Ethylbenzene (C_8H_{10}) $Fe_2O_3.H_2O$, $KClO_3$, $KClO_4$, KNO_3, $Na_2C_2O_4$, NH_3, NO, o-Xylene (C_8H_{10}), SO_2, $Sr(NO_3)_2$ and Toluene (C_7H_8) with human superoxide dismutase (SOD), human serum albumin (HSA), and estrogen related receptor gamma (ERR-gamma) proteins. AutoDock 4.2.6 was employed to perform rigid docking. Against HSA, NH_3 exhibited the least binding energy *i.e*. -5.19 kcal/mol. Against ERR-gamma, Al_2O_3 showed the least binding energy *i.e*., -4.08 kcal/mol. With SOD, ethylbenzene exhibited binding energy of -4.62 kcal/mol. A molecular dynamics simulation of 10 ns was performed on the ERR-gamma-o-xylene complex at 300K at the molecular mechanics level using GROMACS 5.1.2., showing conformational changes within the protein due to the o-xylene binding. The average Root Mean Square Fluctuation of the complex was 0.0821 nm. The results can be further elaborated and may guide future research for the intervention of protein targets for chemical toxins.

Keywords: Air pollution, Health, Hazard, Virtual screening, Protein.

INTRODUCTION

Fireworks burning are reported from all over the world during the festival of Deepawali in India [1], Chinese Spring Festival [2], 4th of July, the Independence Day in the USA [3], Lantern Festival in Taiwan [4], and Guy Fawkes in the United Kingdom [5] (Table **1**).

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Table 1. List of festivals and events that include pyrotechnics and bonfires [14].

Festival/Event	Country	Time of Year	Description
Las Fallas	Spain	March	One of the most significant pyrotechnic festivals in the world is the Las Fallas Festival. With fireworks, processions, music, and gourmet delicacies, Las Fallas illuminates Valencia's old streets every year.
The Lantern Festival	China	February	The streets are lined with colourful lanterns, many of which have riddles engraved on them, during the night of the Chinese Lantern Festival. Tangyuan, or sweet rice balls, are eaten, dragon and lion dances are performed, and fireworks are let off.
Bonfire Night	UK	November	On November 5, fireworks, bonfires, sparklers, and toffee apples are used to mark Bonfire Night in the United Kingdom. They perform it in remembrance of the anniversary of an unsuccessful attempt to blow up the Houses of Parliament.
Tihar	Nepal	October/November	Tihar, also known as Deepawali and Yamapanchak in Nepal, is the second-largest celebration after Dashain. It is a five-day holiday that is predominantly observed by Hindus all around the world.
Sky fest	Ireland	March	The St. Patrick's Day Skyfest fireworks show above the River Liffey in Dublin, Republic of Ireland, is part of the build-up to Wednesday's St. Patrick's Day parade, which takes place in major cities and villages throughout the world.
Bastille day	France	July	On July 14, the anniversary of the assault of the infamous Bastille prison in 1789, events for Bastille Day are customarily conducted in Paris, which was a watershed moment in the triumph of the French Revolution and is now a national holiday throughout France. The stunning fireworks display at the Eiffel Tower on the Champ de Mars begins at 11 p.m. and lasts for 30 minutes.
Diwali	India	October/November	According to Hindu beliefs, the residents of Ayodhya celebrated Lord Ram's return by lighting Diyas or earthen lights, which is how the day got its name, Deepavali or Diwali. There is no historical evidence, however, of when blowing firecrackers became a feature of Diwali festivities.
Australia Day	Australia	January	Australia Day, January 26th is a holiday commemorating the commencement of the first permanent European colony on the Australian continent. Sporting events, like horse races and regattas, have remained an essential component of the celebrations, and the day's festivities frequently conclude with fireworks.

(Table 1) cont.....

Festival/Event	Country	Time of Year	Description
Fourth of July	USA	July	Since its inception in July 1777, fireworks have always been a significant part of Independence Day in the United States, which commemorates the signing of the Declaration of Independence.
New Year's Eve	Worldwide	December/ January	At the stroke of midnight, fireworks and firecrackers are lit to ward off evil spirits and welcome the new year. On the morning of January 1st, some communities have a tradition where families light firecrackers as they enter the house or just before leaving. Throughout the entire year, it represents luck.

The environmental quality, particularly air quality is jeopardized by short-term rise in pollutants and several other hazardous chemicals like potassium nitrate (KNO_3), carbon (C) or sulphur (S). Other than that, many chemical compounds of elements like Ba, Sr, Ti, Mg, Al and Cu [6] *etc*. are used as components of fireworks to bring about different colours [7]. The present chapter reports the *in silico* molecular docking studies of some common chemicals emitted from fireworks and how they interact with prominent human proteins namely human superoxide dismutase (SOD), human serum albumin (HSA), and estrogen-related receptor gamma (ERR-gamma or ERRγ). The study was undertaken to understand the toxicology of chemical compounds emitted from fireworks and how they may interfere with biochemical pathways by binding with target proteins. ERRγ is an important protein which acts as a potential tumour suppressor. It has been found to inhibit gastrointestinal cancer cell growth [8]. Oxidative stress triggers redox-sensitive pathways leading to inflammation and cell death. Particulate matter, especially fine ($PM_{2.5}$, PM < 2.5 μm) and ultrafine ($PM_{0.1}$, PM < 0.1 μm) particles, ozone, nitrogen oxides and transition metals act as potent oxidants and generate reactive oxygen species (ROS) [9]. Superoxide dismutase (SODs) act by creating a defence against oxidative stress in the body. The enzyme acts as a potential therapeutic agent against ROS-regulated diseases [10]. Another important and abundant protein in blood plasma is HSA which transports hormones, fatty acids and other components through the bloodstream. It also maintains osmotic blood pressure. It can interact with several ligands including exogenous pharmacological drugs [11]. The present virtual study was performed to assess the interaction of some of the important compounds released as a result of firework burning with a few selected proteins through molecular docking, which is a method to find out the most preferred orientation of the ligand with the active sites of the selected protein [12]. The best conformation is selected by scoring functions which also predict the binding affinity. The binding helps in understanding the essentials of biochemical processes and may provide a rationale

CHAPTER 9

Computational Nanotoxicology and its Applications

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Abstract: The trial on non-testing approaches for nanostructured materials and the prediction of toxicity that may cause cell disruption is needed for the risk assessment, to recognize, evaluate, and categorize possible risks. Another tactic for examining the toxicologic characteristics of a nanostructure is using *in silico* methods that interpret how nano-specific structures correlate to noxiousness and permit its prediction. Nanotoxicology is the study of the toxicity of nanostructures and has been broadly functional in medical research to predict the toxicity in numerous biotic systems. Exploring biotic systems through *in vivo* and *in vitro* approaches is affluent and time-consuming. However, computational toxicology is a multi-discipline ground that operates *In silico* strategies and algorithms to inspect the toxicology of biotic systems and also has gained attention for many years. Molecular dynamics (MD) simulations of biomolecules such as proteins and deoxyribonucleic acid (DNA) are prevalent for considering connections between biotic systems and chemicals in computational toxicology. This chapter summarizes the works predicting nanotoxicological endpoints using (ML) machine learning models. Instead of looking for mechanistic clarifications, the chapter plots the ways that are followed, linking biotic features concerning exposure to nanostructure materials, their physicochemical features, and the commonly predicted conclusions. The outcomes and conclusions obtained from the research, and review papers from indexing databases like SCOPUS, Web of Science, and PubMed were studied and included in the chapter. The chapter maps current models developed precisely for nanostructures to recognize the threat potential upon precise exposure circumstances. The authors have provided computational nano-toxicological effects with the collective vision of applied machine learning tools.

Keywords: Biomedical, Computational nanotoxicology, *In silico* approaches, Molecular dynamics, Machine learning, Nanostructures.

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INTRODUCTION

The field of nanotoxicology emerged as a novel branch to assess the hazards and probable risks posed by nanoparticles (NPs) and nanostructured materials.Nanotoxicology deals with the prediction of the hazardous effects of nanostructures on the atmosphere and living beings [1]. The main challenge involved in the prediction of nanotoxicity is the dissimilarity among the physiochemical characteristics of the nanostructures and bulk materials (bigger than 400 nm), even after having the same organic configuration [2]. These exclusive characteristics of nanostructures complicate the toxicity assessment. In contrast to the hazards posed by bulk materials, the toxicity of the nanostructures does not correlate with its dosage [3] or chemical configuration.However, the toxicity typically depends on the size, superficial area, external chemistry, crystalline assembly, accumulation in the media, fabrication, and transparency of the nanostructured material [4]. Computational strategies can predict the hazardous effects of the engineered nanostructures. Computational nanotoxicology involves the conjugation of contemporary computation and data expertise with molecular ecology to evaluate the hazardous consequences of nanostructures [5]. Computational methodologies can predict a biotic endpoint precisely. Because of a huge number of chemical constituents, high experimental charges, and limited research facilities, the toxicity profile of many of the chemical substances is not available [6] and that makes, computational nanotoxicology a useful approach. Understanding nanostructures and their interactions with proteins, cell walls, cytoplasm, and intracellular organs is vital for exploring nanotoxicology and associated mechanisms. Considering the complexity associated with the prediction of toxic effects associated with nanostructures that may vary even upon a slight change in the nanostructure. Fig. (**1**) summarizes a general roadmap for the implementation of a model for computational nanotoxicology studies. The roadmap can be dividedinto five key steps: 1) dataset construction overview, 2) data processing, 3) model execution, 4) model authentication and 5) applicability domain [7 - 10].

The computational methodologies can efficiently and accurately define nanostructures and their responsiveness and toxicity [11, 12]. Quantitative structure-activity relationship (QSAR) modeling is used for the predictive toxicology of nanomaterials [13]. With the assistance of computational toxicology methodologies, the AOP (Advanced oxidation process) can be predicted using high-throughput statistics without pre-introducing existing AOPs or knowledge of mechanistic insight [14, 15]. Molecular dynamics (MD) simulation is utilized to investigate the time-dependent competence of a molecular scheme such as the physical arrangements of atoms and molecules [16, 17]. This chapter summarizes several computational methodologies like MD simulation, machine learning tools

in nanotoxicology, nano-QSAR (Nano-quantitative structure–activity relationship) modelling, and, other computational techniques such as molecular docking which are used for studying the toxicological properties of nanostructures.

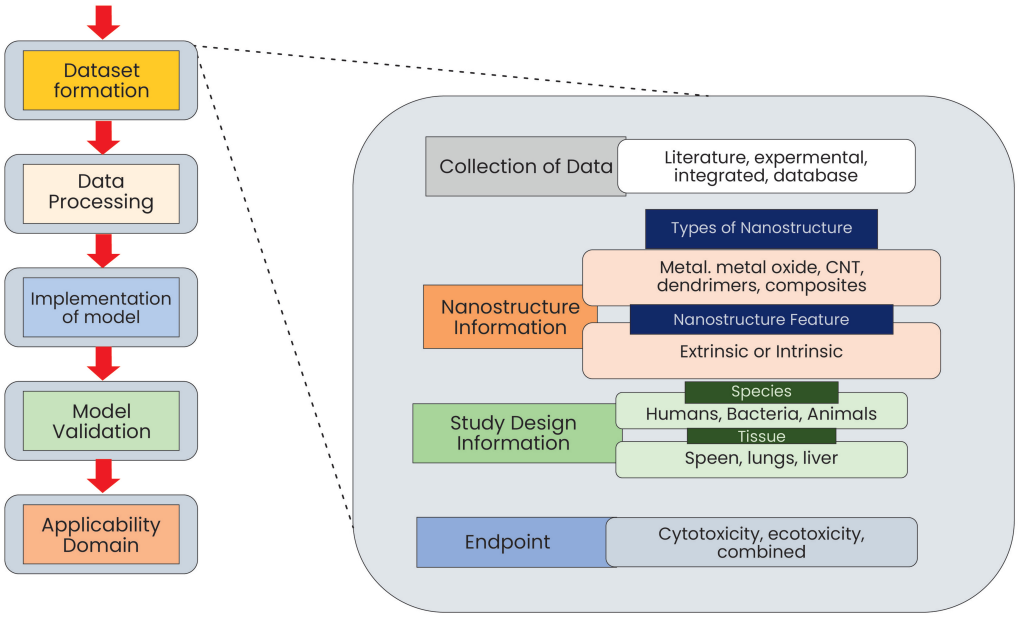

Fig. (1). A brief roadmap of computational nanotoxicology modelling.

POTENTIAL TOXICITY OF NANOPARTICLES

The unique properties of nanostructured materials like their surface area, size, and their behaviour upon interaction with biomolecules, play a key role in toxicity assessment [18]. It has also been established that nanostructures can enter the liver, circulatory system, and central nervous system (CNS) [19, 20]. The interaction between nanomaterials and macromolecules like DNA and proteins needs more studies [21]. Natural nanomaterial surfaces are tremendously responsive towards biomolecules, particularly proteins [22]. When the nanostructures come into contact with the biotic fluids, proteins are deposited on their exterior surface area, identified as the ‘protein corona’. Depending upon the ability of the interface between the protein and the nanostructure’s superficial area, protein coronas have diversified structures, the first one is the “soft corona” which is formed by high copiousness proteins with a rapid active exchange, and the second one is the “hard corona” made up of proteins with a high attraction that can change its physical configuration as depicted in Fig. (**2a**). The arrangement of this protein corona frequently fluctuates upon cellular uptake of the

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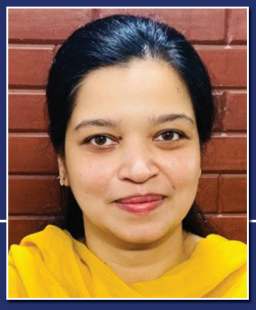
Dr. Tahmeena Khan is currently working as an Assistant Professor, in the Department of Chemistry, Integral University. A gold medallist in her master's course, she holds specialization in inorganic chemistry. She specialized in magnetic resonance spectroscopy and magnetic resonance imaging for her M.Phil. and worked on automated 3D structure determination of proteins for her dissertation. For her doctoral degree, she worked on mixed ligand-metal and mixed metal-ligand complexes of thiosemicarbazones and their therapeutic properties. She holds sixteen years of teaching experience and has supervised several dissertations of M.Sc. students. She has fifty research publications and twenty five book chapters to her credit. She has also edited five books. She is also a life member of several academic bodies. Her research areas of interest include computer aided drug designing and environmental contaminants' assessment and remediation.



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