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In silico nanotoxicology: The computational biology state of art for nanomaterial safety assessments

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ABSTRACT

In recent decade, nanotechnology has got an extensive advancement in terms of production and application of nanomaterials. With the advancement, concern has risen for their biomedical and ecological safety, provoking a detailed analysis of the safety assement. Numerous experimental and computational approach has been developed to accomplish the goal of safety assessment of nanomaterials leading to orgin of interdisciplinary fields like nanoinformatics. Nanoinformatics has accomplished significant strides with the development of several modeling frameworks, data platforms, knowledge infrastructures, and *in silico* tools for risk assessment forecasts of nanomaterials. This review is an attemption to decipher and establish the bridge between the two emerging scientific arenas that includes computational modeling and nanotoxicity. We have reviewed the recent informations to uncover the link between the computational toxicology and nanotoxicology in terms of biomedical and ecological applications. In addition to the details about nanomaterials interaction with the biological system, this article offers a concise evaluation of recent developments in the various nanoinformatics domains. In detail, the computational tools like molecular docking, QSAR, etc. for the prediction of nanotoxicity here have been described. Moreover, techniques like molecular dynamics simulations used for experimental data collection and their translation to standard computational formats are explored.

1. Introduction

The modern era of day to day life activities in industrial and domestic reign results in the production of various types of ultra-fine particles. These activities includes artificial as well as natural process like building construction, metal welding, cigarette smoke, aircraft waste gas, diesel exhaust and wildfires, volcanic eruptions, and other natural processes. The byproducts of these activites along with the production process creates nanomaterials with specific physiochemical properties linked to their micro or nanosized structures. Moreover, these nanomaterials are finding their way in different applications like electronics, cosmetics, pharmaceuticals [1]. According to the nanodatabase recorded till March 2023, 5367 products of day to day activites are integrated with nanomaterials. These nanomaterials are designed with specific properties such as increased strength, catalytic properties, electrical and thermal conductivity, etc dedicated to their requirement in biomedical and social applications. Given the utility of these nanoparticles, the risk assessments of hazardous impact due to their possible exposures is required. Scientists and toxicologist have given special attention to the concern of heath risk and stydying it at different parameters. Oberdörster et al. in 2005, introduced a subfield of toxicology called "nanotoxicology", also recognized as "nanosafety"[23] in concern of the safety assessments of nanomaterials. The field of study is focused on the extent of ecotoxicity and biomedical toxicity of engineered and naturally

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produced nanoparticles.

Conventional experimental techniques and methodologies used for the toxicological investigations have their limitaions due to high cost, time-consumption, ethical concerns, and inability to align with the fast-paced nanotechnology industry [4]. To address the safety concerns of natural and engineered nanomaterials, there is a need of fast and reliable methods that can complement experimental approaches and reduces the number of experiments and resources; owing to fast-paced computational industry and research, it can be achieved by development of high throughput computational assessment methods [5]. The two broad strategies for evaluating the potential hazards of nanomaterials are experimental toxicology; which involves *in vitro* and *in vivo* testing, and computational simulations; which relies on *in silico* analysis [678]. The field of computational chemistry has been broadly accepted and advanced since its inception in 1960 s. With the development of powerful computers and sophisticated algorithms, researchers can now analyze vast amounts of chemical data using a variety of statistical and machine-learning techniques. This has revolutionized drug discovery, materials science, and many other fields that rely on chemical data analysis. The implementation of computational chemistry has allowed the scientists to predict the properties and behavior of chemical compounds before conducting expensive and time-consuming experiments. To be more precise, the computational approaches simulates the the relationships between the structure, properties, and biological effects of nanomaterials as the principal endpoint. Therefore, as recommended by the European Chemicals Agency, reliable computer-generated models can provide additional valauble information during the initial phase of investigations to detect potential nanoparticle-related hazards. (ECHA) [9]. Alternatively, they can help in categorization and labelling of nanomaterials based on the degree of hazardness. To assess the risks of NMs, it is important to classify and determine, the exposure pathways, forms, concentrations, and threshold levels of hazardness of nanomaterials in terms of both biomedical as well as ecotological aspects. These steps also require the integration and assessment of NMs characterization and toxicity data which are currently in disparate. It is imperative that based on purely laboratory studies of the risks associated with NMs, a lot of time, money, and resources will be consumed [10]. Computational methods could provide the solution by understanding the links between NM structure, characteristics, and their biological impacts in fast pace and with reliablility. The quantitative structure–activity relationship (QSAR) technique is the foundation of the most effective computer models that can predict the biological characteristics of NMs in a variety of complex situations. It can model correlations between the material's structure, molecular characteristics, provenance, and their biological effects using statistical and machine learning (ML) algorithms. Recently a number of literature have thoroughly studied the use of the approach for studying a variety of NMs toxicity (Fig. 1) [11].

Even though these approaches are data-driven, they can nonetheless simulate relatively tiny data sets [12]; it is imperative that the more extensive models will boost the automation of processing and interpretation of experimental data based on larger data sets.

These computational models can be used independently and can also be used as input parameters for more intricate pharmacokinetic (PBPK) models based physiological studies. The simulations can then be run using the information on QSAR and can foretell biological activities through estimation of probable biological interaction partners which can be responsible for hazardous response. These computer methods can quickly close data gaps, take use of "read across" predictions of the biological effects of related materials, and categorize the risks posed by NMs to different species. Additionally, they are helpful supplements to experimental data on the biological characteristics of novel materials, which continue to be the principal obstacle for accurate risk assessment [13]. These kinds of *in silico* models are widely used by researchers in both academia and industry to calculate PChem properties precisely for the assessment of the effects of chemicals on human and environmental health and predict the fate of a wide range of chemicals, including complex materials. Moreover, integrating these data resources across different disciplines; including non-nanotechnology resources and methodologies like chemoinformatics, systems biology, and omics; will assist in achievement of other goals like the reuse of existing data[14]. For continuous advancement in nanosafety research, an authenticated, predictive *in silico* method that can deliberates the complexity of NMs and their deploying area is necessary. Additionally, a thorough analysis can result fresh study findings that can energize the pipeline for new innovation. In past years, a wide range of computational techniques have been created in an effort to enhance simulations and generate accurate findings. Considering the recent advancements in computational biology, this review aims to discover "*in silico*" based assessments that have contributed to a better understanding of safety assurance allied with recently discovered nanomaterials.

2. Bio-nano Interactions: A mechanistic approach to nanoparticle toxicity

The nantechnology has shown an enormous potential in the revolution of biomedicine,and creation of sustainable environmental technologies. Unlike larger molecules, nanoparticles can access far more remote locations in the human body owing to their small size and higher surface area, aiding to the several physiological benefits like extended circulation, efficient controlled release of drugs, and blood–brain barrier crossing abilities[15]. The incorporation of established medications with nanoparticles enables their direct delivery to the targeted tissue, improving the effectiveness of the chemotherepy and optimization of the dosage. However, the application of nano-medicine in clinical

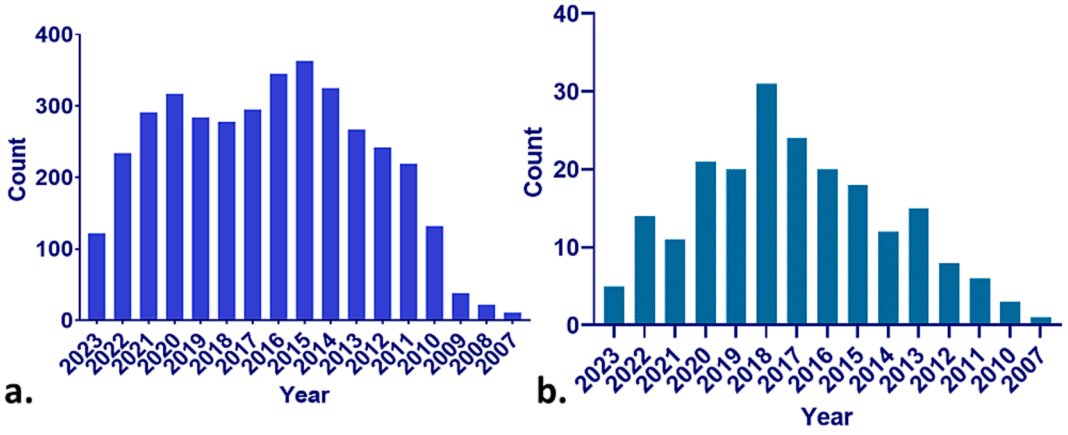

Fig. 1. Bar graph showing the recent publication trends in the field of (a) Nanotoxicology and (b) computational nanotoxicology as estimated by pubmed analysis.

settings is hindered by the lack of understanding of the interactions between nanomaterials (NMs) and biological microenvironments. Thus, a systematic evaluation of nano-bio interaction is required for the efficient designing of safe and reliable NMs for biomedical applications [16]. Cabrera et al. has reported an experimental research on the interactions between low-cost IONPs (bare iron oxides, silica-coated surfaces, or readily functionalized surfaces) and the four main classes of biomolecules—proteins, lipids, nucleic acids, and carbohydrates. The driving forces and interdependending governing interactions at the solid–liquid interface, the distinctive structural traits of each class of biomolecules, and the environmental factors affecting adsorption were given special consideration[17]. In order to outline the bio-nano interface, three crucial frontiers are frequently taken into account: (1) the surface of the nanoparticle, which is distinguished by its physicochemical characteristics[18]; (2) the biological material, which converges with the solid–liquid interface at the contact plane; and (3) the surrounding environment, which along with the particle forms the solid–liquid interface[19]. The first element shaping the bio-nano interface is the nanoparticle itself. For studying these interactions, a thorough characterization and comprehension of the nanoparticle qualities are essential because the identity of the different components is determined by their intrinsic characteristics. [2021]. The second component at the bio-nano interface is the target biomolecule, which has unique properties and a variety of forms, charges, sizes, and conformations in complicated mixes (Fig. 2). These characteristics specify the interactions with organic and inorganic materials and the specific functional groups exposed in the medium around them. The third building block is the medium of the interface. Its significance comes from its capacity to change the inborn properties of nanoparticles and biomolecules, including surface charge (zeta potential), stability (biodegradability), hydration, valence state, and capability to transport electrons[18] (Fig. 3). At the bio-nano interface, physical–chemical interactions occur between the surface of nanoparticles and biological compounds (Fig. 2). Firstly, the forces collaborating in the interaction between nanoparticles and biomolecules appear to be alike to those in classical colloidal systems[22]. Both physio-sorption and chemisorption can be used to categorize these interactions[19]. While chemisorption occurs when electron sharing occurs at the binding site developing stronger links (e.g., covalent bonds or hydrogen bonds), typically, physio-sorption depends on the attraction of the adsorbing elements for the surface while remaining chemically unchanged (e.g., van der Waals, electrostatic, and so-called hydrodynamic interactions) [17]. With an advancement of implication of nanotechnology and nanomaterials in different applications, the abundance and concentration of NMs has also increased,

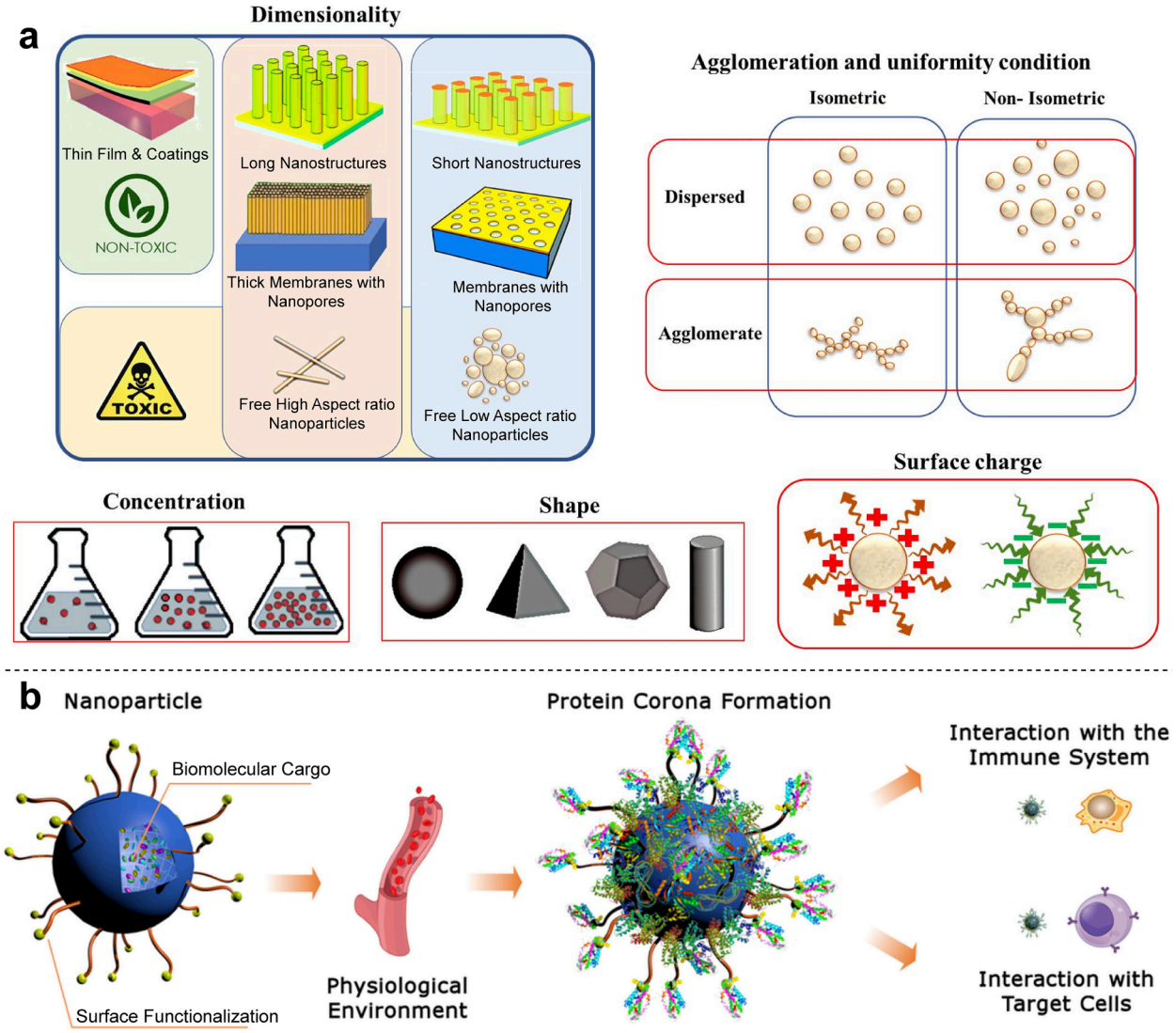

Fig. 2. (a) Physical properties of metal oxide nanoparticle playing crucial role in the nanotoxicity (Image adapted from [23]) (b) Protein corona formation and interaction with immune cells (Image adapted from [24]).

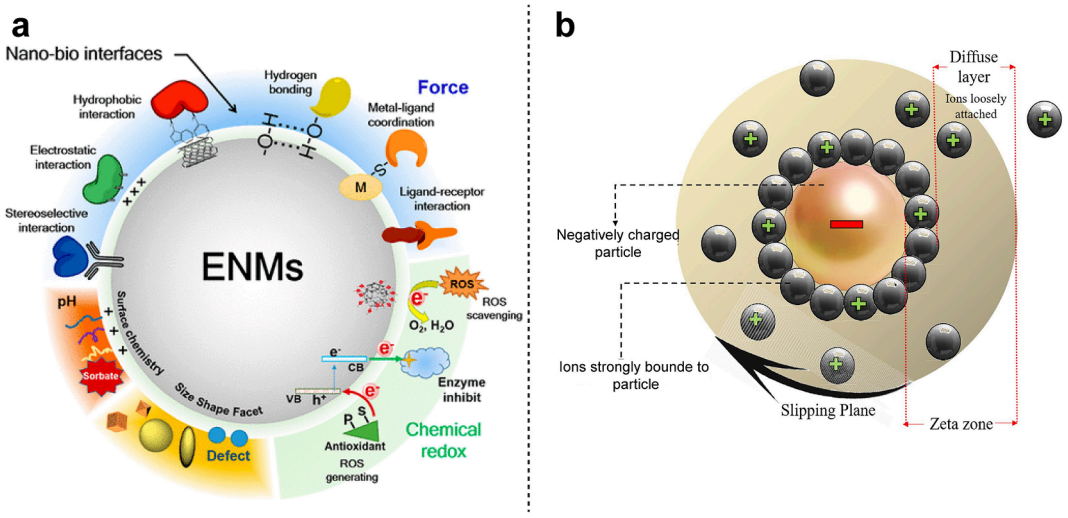

Fig. 3. (a) Nano-bio interactions and the driving forces (Image adapted from [31]) (b) Zeta potential zone and electric double layer surrounding charged nanoparticles shown schematically (Image adapted from [23]).

attracting significant attention of worldwide reserachers to the toxicological concerns of these NMs. This has led to the foundation of new research topics like "Nanotoxicology", studying about the pathophysiology and toxicity of NMs influenced by the formation of the biomolecule corona[25] (Fig. 2). Consequently, a number of studies on the function of the biocorona have been carried out, albeit with divergent outcomes. An investigation by *Docter et al.*[26] suggested that the protein corona played a significant role in cellular absorption and toxicity. Here, *in vitro* studies demonstrated that the corona-formation is responsible for a decreased cellular uptake of NMs in addition to the size factor of NMs involved in cellular toxicity[26]. Additionally, the NM-protein corona complex is required for NMs to induce or modify immune responses, thereby activating the immune system. For the safe use of NMs in medicine, it is crucial to comprehend nano-immune interactions[27]. In another study, researchers used primary human blood system cells in *in vitro* research to show the (patho)-biological effects of the protein corona. Here, protein-coated NMs exhibited less toxicity compared to pristine NMs, indicating that the corona protects cells from the NM-induced (patho)-biological processes and can also promote cellular uptake[25]. Apart from above mentioned reports, there is also an upsurge in the number of studies using computational approaches to address the relation between different NMs and biomolecules[28].

NMs interactions with biomolecules and structures (such as peptides, proteins, phospholipids, nucleic acids, etc.)[29] plays important role in different biomedical applications[30]. In order to control the reactions at nanomaterial-biology (nano-bio) interfaces, it is crucial to assess the fundamental mechanisms underlying these processes. The three primary elements involved in the phenomenon are: (1) biomolecules adhering to NM surfaces to form protein corona; (2) reconstructing and altering functional proteins; and (3) redox reactions between NMs and reactive species [16]. A case-by-case method of nano-toxicity evaluation is impractical due to the large amount of dataset obtained because of the variability of NMs physiochemical nature. High-throughput techniques might become essential tools for closing existing information gaps in our understanding of engineered NMs and their biomedical and ecological impacts.

3. Nano-toxicology and computational biology: a brief introduction

Just like every other attributes on this planet, nano-formulations too have their pose and cones. Nano-toxicity can be considerd as the darker side of nano-formulations, and has become a major challenge in the field of nanoscience and nanotechnology. Chemotherapeutic medications, nano-medicines, and nano-carriers all have hazardous profiles. When a nano-carrier containing bioactive (protein and peptide medicines) and chemotherapeutic medications (anticancer agents) is exposed to the body over an extended period, it becomes toxic and selectively induces cytotoxicity in healthy cells and organs (Fig. 4). Nanotoxicology is a relatively young field that embraces advances in toxicology, such as the use of systems biology techniques to simulate and foresee the disruptions caused by NMs in living systems. A comprehensive understanding of nano-bio interactions can only be attained through a combination of different perspectives found in chemistry, physics, molecular biology, immunology, pharmacology, computational sciences, and other fields [32]. This is why it is important to view nano-toxicology as an interdisciplinary lesson. Therefore, constant communication between scientific disciplines is crucial. The primary focus of nano-toxicology is the toxicity of nanoparticles and determining their toxic effects on individuals and the environment. Silver[3334], Gold[35], Cobalt oxide [36], Titanium dioxide[3738], Magnesium oxide[39], Iron oxide[40], Zinc oxide[41], diesel exhaust nanoparticles, as well as carbon nanotubes, fullerenes[42], and "nano-C60″ are typical nanoparticles that have been extensively studied in various toxicological studies[43]. Therefore, communication between scientific disciplines is very crucial [44].

By the late 1950s, computers were already used in population studies, species classification, and taxonomy construction; where programs, however, merely served as sophisticated calculators. The background for systems biology was largely hypothetical and not especially algorithmic, even though Wiener and others' work on cybernetics created the foundations for it. The first bioinformatics algorithms were created at roughly the same time as theoretical computer science was still a fledgling discipline. Following the invention of Sanger sequencing, new algorithmic design and analysis concepts in dynamic programming—for example, by Levenshtein for the computation of edit distance—and data structures for string matching—for example, the suffix trees of Weiner and McCreight—benefited the first computational methods for genomic and proteomic sequence similarity search as well as RNA secondary structure prediction. The Human Genome Project's launch in the 1990s led to a sharp surge in algorithmic activity for resolving biomolecular issues. This period saw the emergence of novel techniques for multiple sequence alignment, motif discovery, haplotyping, phylogenetic tree construction, protein structure analysis, and prediction, all of which helped to set the stage for the ultimate completion of the human genome sequence. The pursuit of assembling

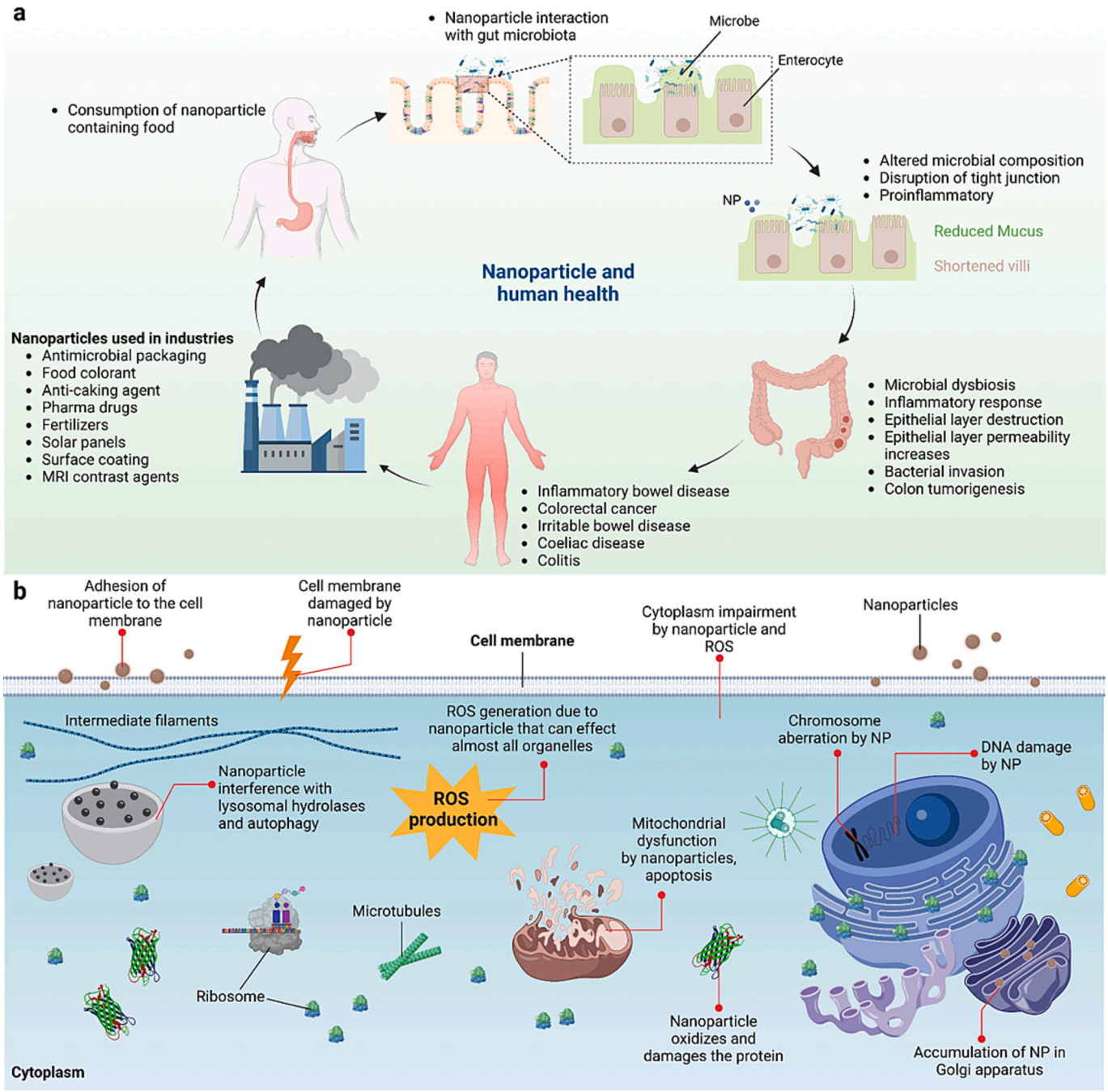

Fig. 4. Toxicity of nanoparticles: (a) Released nanoparticles from various sources and their harmful effect on human health (modified and conceptualize from [45]) (b) Nanoparticle induced toxicity mechanism (modified and conceptualize from [23]).

the human genome from Sanger sequencing reads by both public and private initiatives in the late 1990s was particularly fascinating. Numerous statistical and combinatorial techniques for clustering, classification, and regression have been developed concurrently with microarray technology development. By extending systems biology into the field of network science, additional developments in co-expression analysis and protein interaction prediction were made using the yeast two-hybrid system. Bioinformatics entered a new age of Big Data science with the completion of the Human Genome Project and the introduction of next-generation sequencing technology. The use of RNA-Seq data in read mapping and variant detection algorithms, gene annotation and functional element discovery methods, gene expression, and alternative splicing analysis tools, as well as the 1000 Genomes Project, ENCODE and mod-ENCODE, The Cancer Genome Atlas, and the International Cancer Genome Consortium, became essential to large-scale international scientific projects. Interconnections between molecular biology, theoretical computer science, statistics, and statistical machine learning will need to get more intricate as the number and variety of biomolecular data increase. Although algorithmic technology from the 1980s and 1990s, such as suffix arrays, locality-sensitive hashing, and color coding, as well as general methods for linear and non-linear optimization and approximation algorithms for NP-hard problems, have already found significant applications in bioinformatics; more recent methods such as streaming, sketching, metric embeddings, compressed data structures, differential privacy, homomorphic encryption, and others have yet to do so. Similarly, the theoretical computer science community has paid little attention to new issues in large data genomics, transcriptomics, and proteomics.

Similarly, the theoretical computer science community has paid little attention to new issues in large data genomics, transcriptomics, and proteomics. Computational biology utilizes data analysis, mathematical modeling, and computer simulations to understand biological systems and interactions. Fig. 5 illustrates the computational tools used for the nanotoxicity analysis. The field is a junction of computer science, biology, and big data with origins in applied mathematics, chemistry, and genetics. It differs from biological computing, a subfield of computer engineering that uses bioengineering to build computers.

4. *In silico* approaches for toxicity-based assessments

Several *in silico* models and methods have been used to assess and predict the potential toxicity of chemical substances and their associated risks to humans and the environment. The different toxic effects of industrial chemicals have led to an understanding of the value of combining *in silico* models in risk assessments. Through a thorough assessment of chemicals, it is critical to identify and manage hazardous materials in advance[46]. Previously, the entire procedure of identifying hazardous substances depended on conducting tests on animal models. To avoid sacrificing thousands of animals, a cost-effective *in silico* approach can be helpful[47]. Additionally, utilizing non-testing methods to foresee toxicity early in the drug discovery and development cycle helps to reduce costly drug failures caused by toxicity being discovered in late development or even during clinical trials.

A wide range of computational tools are currently in use for *in silico* toxicology, for instance, databases, programs that produce molecular descriptors, simulation tools, and modeling techniques. Based on the idea that a substance's molecular characteristics can be correlated with its physical and biological properties, *in silico* models and tools can predict the efficacy and toxicity of a substance. A few of the major *in silico* models used for toxicity-based assessments and hazard management are QSAR, Read-Across, and Expert Knowledge Models.

Each year, the nanomaterials scientific community implement quantitative structure–activity relationships (QSARs) predictions for the toxicity assessment of thousands of chemicals, [48]. In silico toxicity analysis aims to forecast chemical toxicity, which use a range of computational techniques to link a chemical's structure to its toxicity or efficacy through computational modeling, QSARs, and algorithmic prediction. Finding the best approach for each problem of chemical toxicity is crucial because of the need of unique scope and interpretation intepreting the advantages and disadvantages of the methods[49]. Risk assessments frequently ignore the negative effects of the mixture, which is how chemicals become toxic when they interact with other substances. Moreover, it is also difficult to asses the synergistic toxicity of the mixture elements [50]. Quantitative structure-nanotoxicity relationships, also known as quantitative structure-nanotoxicity relationships (QSNR), or nano-QSAR, are unique to nanomaterials and include characteristics like size, shape, surface area, and solubility. A linear QSNR model has been developed to predict the effective concentration for 50 % enzymatic inhibition (EC_{50}) of AgNPs from their data of size and surface charge[46]. Integrating high-throughput screening techniques with biosafety and *in silico* modeling emphasizes a system biology approach that guarantees the quality of nanosafety research, fills the mechanical gap in fundamental research, and offers suggestions for predictive biological responses in nanotoxicology. However, "nano-QSAR" needs to be organized and standardized with the data gathered for nano-characteristics. The NanoPUZZLES project of the EU was one of the international collaborations that improved the data availability and modeling approach to support the evaluation of nanomaterials. System interactions should be considered when developing toxicity prediction models[51].

A significant problem in the study of toxuicological evaluations is the prediction of chemical toxicity *in silico* using machine learning and structural alerts, including the various toxicities and negative effects. [52]. There have been efforts to create *in silico* models, including computational tools, that can be used to predict the toxicity of compound before being syntheticlly synthesized. Chemical risk assessment has recently seen the development of chemical toxicity prediction models, as well as an admetSAR Web server with machine learning techniques and structural alerts that have been created for free public use[53]. For instance, recently CarcinoPred-EL, a Web server that can predict carcinogenicity online, was created to model chemical carcinogenesis[54]. There are currently over 8000 compounds that are known

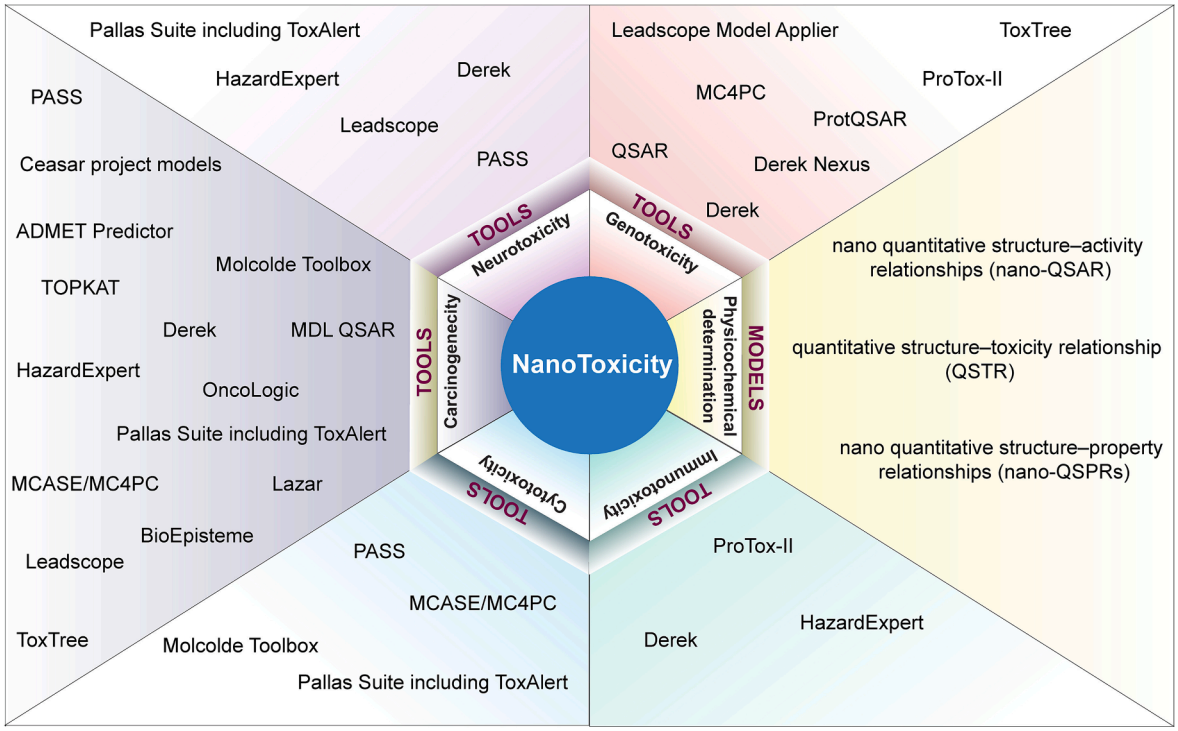

Fig. 5. Computational tools and models used for nano/toxicological analysis.

to be Ames mutagens, and in toxicity data have been used to expand predictive models and structural alerts recent years. The most frequently studied computational prediction is acute oral toxicity, for which computational models have been created (Table 1). A variety of machine learning techniques were created and used to build classification and regression models to forecast LD_{50} or its toxicity categories[5556]. Considering the near future, computational methods are likely to develop models for unique and novel types of toxicity endpoints for chemicals, provide insight into toxicological pathways, combine and compare results from various models, tailor models to users' needs, and improve models with the availiability of new data.

5. Computational tools assisted toxicity studies

5.1. Molecular docking for structure knowledge

The engineered and natural nanomaterials cause cytotoxicity to the cells due to their surface-to-volume ratio property, which eventually interacts with the macromolecules in a biological system[57]. The interaction and dynamics of the interaction of nanoparticles and the biological system are crucial to understand the mechanism [16]. To obtain insightful predictive interactions, computational analyses like electronic structure methods using molecular docking, density functional theory calculations, Monte Carlo, kinetic mean field model, and coarse-grained molecular dynamic simulations play an important role [58]. The mechanism behind the possible pathological phenotypic changes due to the physiological alterations caused by the nanoparticle interaction with the biological system is not fully understood. However, the modern molecular docking approaches specifically statistical modeling and machine learning method have acquired a stronghold in the macromolecule-nanoparticle interacting prediction.

To simulate the predicted interaction between the nanoparticles and the macromolecules, molecular docking modeling often involves multiple steps (Fig. 6). To replicate the accurate size and shape of the nanoparticle, the structure must first be meticulously constructed. The initial chemical configuration of the nanoparticles may be created from scratch employing various software modules like Material Studio[59], and Chem Draw[60] or it could be retrieved from internet-based databases like the Cambridge Cluster Database[61]. Following that, employing the proper method and degree of theory, the geometry of those nanoparticles must be optimized by minimization of energy. Recently published research has made extensive use of software modules for NP optimization. Gaussian, Forcite, and CASTEP are a few examples. In 1970, Carnegie Mellon University created the general-purpose computational chemistry software program known as Gaussian. According to Kumari *et al*[62] and Wu *et al*[63], it can do semi-empirical, DFT, and ab initio calculations as well as molecular mechanical predictions employing specific force fields. According to Arami *et al.*, [59], Forcite is a traditional molecular mechanic tool that may optimize systems of periodicity and structures of crystals while maintaining crystalline integrity. For modeling the properties of solids, interfaces, and surfaces of diverse material groups, including ceramics, semiconductors, and metals, CASTEP is an ab initio quantum mechanics program that relies on DFT computations[64].

Most computational studies use NPs that are less than 100 nm in size and come in an array of structures, including sheets[65], lattices[66], and spheres[67]. In addition, some research has focused on single units as tiny as angstroms, which is a scale commonly encountered in the actual world. It is important to carefully replicate the main dimensions and shape of the Nanoparticles in biological fluids while preparing the Nanoparticles architecture. According to Brancolini *et al*[68], certain NPs, like gold, have the propensity to combine fast in solution. To predict the binding mode, the docking program should be given a meticulously developed, parametrized representation of the actual structure of the nanoparticles under biological environments. As was previously indicated, accurate NPs might be gathered from databases like the

Table 1
List of commercially and freely available software used for predicting toxicological endpoints.

Softwares	Developers	Avaialability	Toxicity endpoints
ACD/Tox Suite	ToxBoxes	Commercial	Acute oral toxicity, Genotoxicity, Endocrine activity
Derek	Lhasa Ltd	Commercial	Genotoxicity, Carcinogenicity, Reproductive toxicity, Endocrine activity, Hepatotoxicity, Nephrotoxicity, Neurotoxicity, Immunotoxicity
BioEpisteme	Prous Institute for Biomedical Research	Commercial	Carcinogenicity, Nephrotoxicity, Hepatotoxicity
ADMET Predictor	Simulations Plus Inc.	Commercial	Chronic oral toxicity, Genotoxicity, Carcinogenicity, Endocrine activity, Hepatotoxicity
HazardExpert	CompuDrug	Commercial	Genotoxicity, Carcinogenicity, Neurotoxicity, Immunotoxicity
Caesar project models	Mario Negri Institute	Free	Genotoxicity, Carcinogenicity, Reproductive toxicity
MCASE/MC4PC	MultiCASE	Commercial	Acute oral toxicity, Chronic oral toxicity, Carcinogenicity, Reproductive toxicity, Endocrine activity, Hepatotoxicity, Nephrotoxicity, Cytotoxicity
OncoLogic	US EPA	Free	Carcinogenicity
Lazar (*In Silico* Toxicology)	Freiburg university	Free	Chronic oral toxicity, Genotoxicity, Carcinogenicity, Hepatotoxicity, Human liver toxicity
OASIS-TIMES	Laboratory of Mathematical Chemistry, Bourgas University	Commercial	Genotoxicity, Endocrine activity
Leadscope	Leadscope	Commercial	Genotoxicity, Carcinogenicity, Reproductive toxicity, Hepatotoxicity, Nephrotoxicity, Neurotoxicity
TerraQSAR	TerraBase	Commercial	Acute oral toxicity, Endocrine activity
MDL QSAR	MDL	Commercial	Acute oral toxicity, Chronic oral toxicity, Carcinogenicity, Reproductive toxicity, Hepatotoxicity, Nephrotoxicity
TOPKAT	Accelrys	Commercial	Acute oral toxicity, Chronic oral toxicity, Genotoxicity, Carcinogenicity, Reproductive toxicity,
Molcode Toolbox	Molcode Ltd	Commercial	Chronic oral toxicity, Genotoxicity, Carcinogenicity, Endocrine activity, Cytotoxicity
Pallas Suite including ToxAlert, Cytotoxicity	CompuDrug	Commercial	Genotoxicity, Carcinogenicity, Neurotoxicity, Cytotoxicity

(*continued on next page*)

Table 1 (*continued*)

Softwares	Developers	Avaialability	Toxicity endpoints
Toxtree	JRC	Free	Chronic oral toxicity, Genotoxicity, Carcinogenicity
T.E.S.T.	US EPA	Free	Acute oral toxicity, Reproductive toxicity
CSGenoTox	ChemSilico	Commercial	Genotoxicity
q-Tox	Quantum Pharmaceuticals	Commercial	Acute oral toxicity
PASS	IBCRussian Academy of Medical Sciences, Moscow	Free	Genotoxicity, Carcinogenicity, Reproductive toxicity, Hepatotoxicity, Nephrotoxicity, Neurotoxicity, Cytotoxicity, Embryotoxicity

Cambridge Cluster Database or drawn *in silico* using data from experiments like nuclear magnetic resonance and dynamic light scattering [69]. There are a number of databases that offer experimental results for typical nanoparticles, including InterNano, Nano-EHS, Nano- HUB, and NANO by Springer Nature[69]. Since, gold nanoparticles have a mean diameter of 12 nm whereas the protein's mean diameter is only 3 nm, researchers from Heidelberg University hypothesized that the protein interprets gold nanoparticles as flat surfaces[68]. The precision of the docking results, however, might be compromised by excessive NPs structural simplification. A single three-atom molecule of titanium dioxide (TiO_2) was utilized for the docking simulation in recent research on the interaction between titanium dioxide nanoparticles and human serum albumin[70]. According to a study by Fei Yin *et al.*[71], TiO_2 NPs often have a rutile or anatase crystalline structure, in which the titanium is coordinated by 6 oxygen atoms in an octahedral configuration. The reduced complexity in this scenario might invalidate the docking results since it distorts the true nature and size of TiO_2 nanoparticle. The biological macromolecule must be prepared similarly. The RSCB Protein Data Bank (PDB) is often used to retrieve the proper crystal structure. If not, a homology model must be constructed with the proper software, such as Swiss-Model, Modeler (BIOVIA), and Prime (Schrodinger). Notably, in the availability of an appropriate crystal structure, homology modeling should be disregarded since it represents still another approximating degree[72]. The ligand and macromolecule are prepared, and then the program of choice is used to complete the docking procedure. It's important to note that there are currently no dedicated programs available for NP docking simulation. The AutoDock program with the Lamarckian genetic algorithm has been employed in the majority of current studies[73]. Additionally, NPs docking has lately made use of various online docking servers. These include Patchdock, which utilizes an algorithm based on shape complementarity[74], and HEX 6.3, which applies an algorithm based on the Fourier transform[74]. Additionally, we have observed that the majority of the published research employed a rigid docking technique that kept the protein

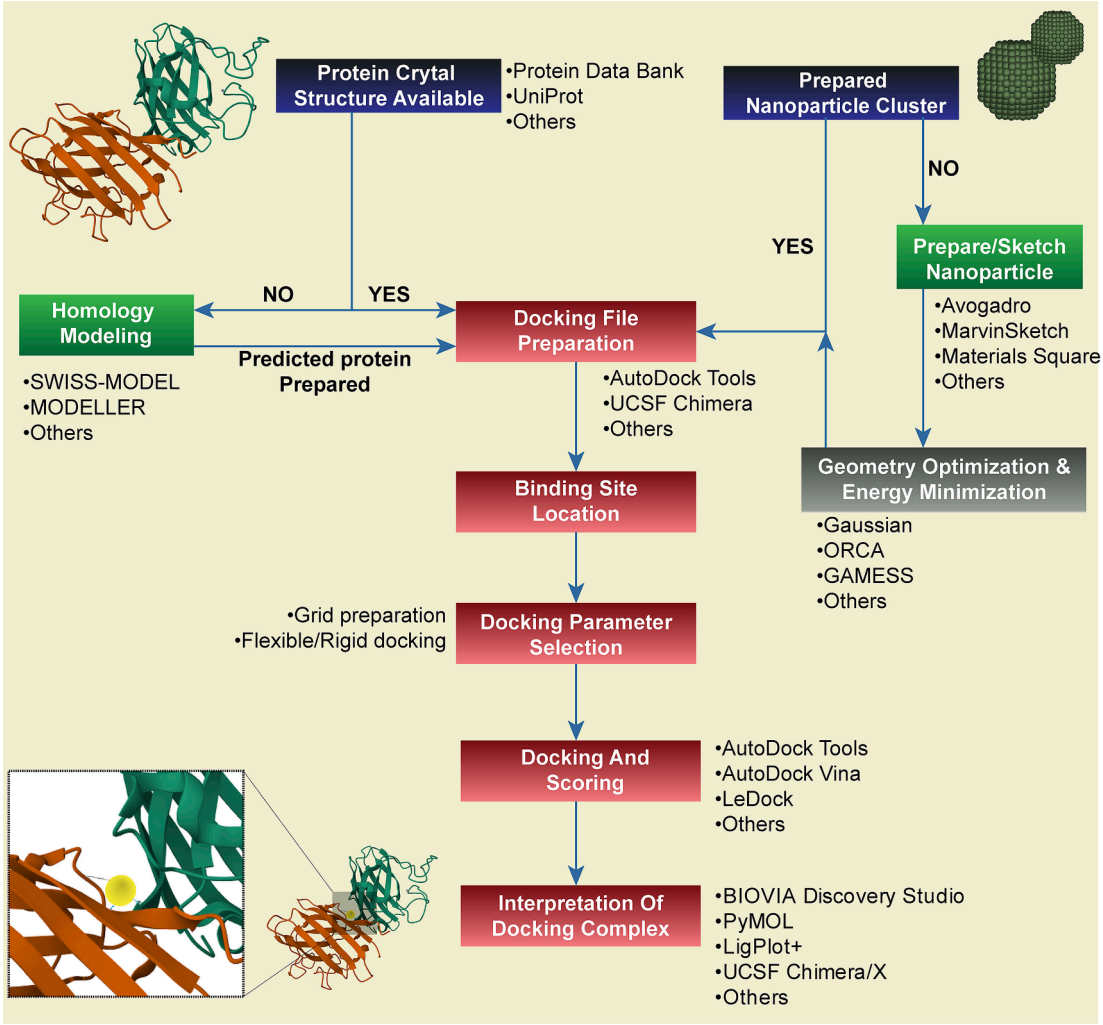

Fig. 6. Schematic representation of steps involved in molecular docking mentioning the tools to perform the molecular docking.

residues at a fixed value. The visualization of the interaction between NPs and macromolecules using several platforms, including Discovery studio, Pymol, iGEMDOCK[75], and UCSF Chimaera[76], constitutes the final phase.

5.2. Quantitative Structure-Activity relationship (QSAR)

The most pursued methods to estimate the toxicity caused by nanomaterials are structure-based mathematical models, particularly quantitative structure–activity relationships (QSAR) at the nanoscale (nano-QSAR)[77]. Examples of these models also include Bayesian methods and Markov Chain Monte Carlo simulation. Numerous QSAR prediction models have been built for predictions of various toxicological endpoints based on molecular descriptors, such as the descriptors generated by Mold2[78], which utilized the innovative methods developed in the structure elucidation system ESSESA. The fundamental goal of a QSAR model is to specify a suitable function that has an apparent connection between chemical structure and biological activity. In order to forecast toxicity repercussions or create perfect nanomaterials, this may further summarise the physiochemical and biological data[79].

The limitations of conventional QSAR techniques for nanomaterials can be overcome using a variety of other models[10]. The computational hybrid nano-QSAR model for nanocytotoxicity uses two descriptors: electronegativity, which is connected to stability, and the enthalpy of a formation, which is related to bandgap energy. The cytocompatibility of metal oxide ENMs was accurately calculated using the straightforward nano-QSAR method for a variety of cell lines[80]. Under the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulation, the European Commission has started a number of projects to promote the development of computational tools for the evaluation of toxicity caused by engineered nanomaterials (ENMs)[10]. A safe regulation is supported by the fact that several of the evaluated nano-QSAR models can also forecast the bio persistence of the ENMs[81]. Fiber forms of materials and their ability to produce ROS are considered to be signs of a material's high toxicity. All CNTs have a fiber form, however, some also release ROS, in order to investigate the toxicity of MWCNTs, quasi-QSAR models[82] were created based on the representation of conditions, including concentration, the presence of S9 mix, the type of MWCNT (surface area), and the use of preincubation, in a quasi-simplified molecular input-line entry system (SMILES) form, whose descriptor correlation weights were determined via the Monte Carlo method. In an alternative investigation, genotoxicity was modeled as a function of five factors: particle type (MWCNT or fullerene), illumination, concentration, metabolic activation, and preincubation, which produced acceptable statistical values. These examples use the reverse mutation test (TA100) as the cytotoxicity assessment endpoint. Fourches *et al*[83] took into account four empirically discovered descriptors of 44 distinct nanoparticles (NPs): size, zeta potential resulting from the intensity of charge on the surface, R1 relaxivity, and R2 relaxivity. The last two terms have relevance to the magnetic features of the NPs, which affect their capacity to modify the proton spin relaxation rates in the surrounding water molecules. To gauge cellular absorption, they also examined the lipophilicity dataset. The efficiency of the QSAR approach and support vector machines (SVM) in predicting nanotoxicology and developing safer NPs was examined by the authors[84]. To construct and integrate the naive Bayesian classifier on the same dataset, a different study uses the nano-SAR model[84]. Additionally, studies have found that their estimates of cytotoxicity in NPs were more than 90 % accurate. Considering three descriptors;molar volume, size, and polarizability of NPs; Luan *et al*. built a QSAR-perturbation model to forecast the cytotoxicity of NPs against mammalian cell lines and reported an accuracy of 93 %[85].To anticipate the general toxicity profiles of NPs, Concu *et al.* created a unified *in silico* machine learning model based on artificial neural networks. This model's accuracy was greater than 97 % when applied to 260 NPs utilizing two families of descriptors: physicochemical and 2D topology[86]. Based on the outcomes of metal NP first principal computations, Boukhvalov and Yoon created descriptors[87]. They took into account two processes: water dissociation on crystal surfaces with varied miller indices, such as (0 0 1) and (1 1 1), nanorods, and two cubic nanoparticles of 0.6–0.3 nm size made of various metals, including Al, Fe, Cu, Ag, Au, and Pt. The investigations described how the form and size of NPs affected chemical activity. According to the size and specific surface area of NPs, three types of cluster NPs—monometallic (Au-Pd) clusters, core–shell particles, and bimetallic clusters (Au/Pd)—were tested for toxicity on *Escherichia coli* and *CHO-K1* cells[88]. In comparison to pure TiO_2, bimetallic clusters (Au-TiO_2, Pd-TiO_2, and Au/Pd-TiO_2) were found to have increased cytotoxicity. A mathematical model was created using quasi-SMILES descriptors obtained with the Monte Carlo method and the cytotoxicity data of C60 NPs towards Salmonella typhimurium from ref.[89], and the model's statistical parameters were $R^2 = 0.755$ and $q^2 = 0.571$. In order to continue the investigation, two datasets from reference [61] were used, and mathematical models were built as functions of dose, S9 mix, and illumination using quasi-SMILES optimum descriptors discovered using the Monte Carlo approach. In contrast to the preceding study's single split, this study made many splits into the training, calibration, and validation datasets. The reverse mutation test, either TA100 or WP2 uvrA/pKM101, served as the cytotoxicity endpoint in each of these experiments[90]. Similar to the method used earlier, a mathematical function of size, concentration, and exposure duration was used to construct a predictive model for estimating the cytotoxicity of 20 and 50 nm silica NPs. Three random sets—training, calibration, and validation—were created from the dataset. Using the 3-[4,5-dimethylthiazole-2-yl]- 2,5-diphenyltetrazolium bromide (MTT) assay to measure the viability of cultured human embryonic kidney cells exposed to various doses of silica NPs, the toxicity was determined. Cell viability was used as the endpoint in this study's cytotoxicity tests. A collection of experimental data on cytotoxicity encompassing 19 data points for silica NPs was used to compare the quasi-QSAR method (using quasi-SMILES optimum descriptors) with the random forest (RF) approach. Aspect ratio and zeta potential were discovered to be the most significant variables for RF, but no equivalent conclusion could be made for quasi-QSAR. It was also shown that silica's cytotoxicity may be modeled using the RF technique [14]. Later, using CORAL software, better nano-QSAR models with high determination coefficients (0.8–0.95) were constructed based on quasi-SMILES.

5.3. Concept of Grouping/Read-Across

From 2007, the EU implemented REACH, a new paradigm for chemical assessment that includes the staged registration and evaluation of all currently used chemicals that have been produced and imported without safety information. According to REACH Annex XI, Read-across is a method for predicting endpoint data for one or more target substances using data from the same endpoint from other substances which have similar physicochemical, toxicokinetic, toxicodynamic, and ecotoxicological properties, or follow a regular pattern as a result of structural similarity that enables them to be considered a group[91]. Nanomaterials (NMs) lack a clearly defined structure; hence it is more difficult to distinguish them from regular chemicals when it comes to structural similarity. Concerning the application of QSARs and grouping approaches to NMs, as well as how to support grouping for read-across between nanoforms of the same substance, ECHA published a guidance document on information requirements and chemical safety assessment [92]. The ECHA Group Assessing Already Registered Nanomaterials (GAARN) and the ECHA Nanomaterials Working Group (NMWG), as well as an earlier strategy (RIVM, JRC, and ECHA, 2016), have all been considered in the development of this guidance. These concepts and considerations are key to NM grouping and read-across. This includes the requirement to consider characteristics other than chemical composition for instance, aspect ratio, particle size, shape, or solubility,

the affirmation of the similarity requirements from REACH Annex XI for NMs, and the significance of toxicokinetic studies, in grouping, read-across, and for extrapolating from *in vitro* to *in vivo*[93]. Similarly, the Regulatory Cooperation Council (RCC) of the United States and Canada has created a strategy based on the chemical composition which defines seven classes of NMs: semiconductor quantum dots, inorganic carbon, metal and metalloid oxides, metals, metal salts, and metalloids, carbon nanotubes (CNTs), and organics and other classes. RCC defines a flowchart to categorize various groups of NMs according to solubility, biopersistence, and morphology, based on the likelihood of exposure and accessibility of toxicity tests. The flowchart is based on solubility, biopersistence, and morphology[94]. According to Hansen *et al*[95] NMs are classified according to their shape for instance, high aspect ratio NMs are prioritized in terms of hazard or by the presence of toxicological effects for instance, acute toxicity, genotoxicity, mutagenicity, and carcinogenicity (Fig. 7). In conclusion, utilizing the read-across method,

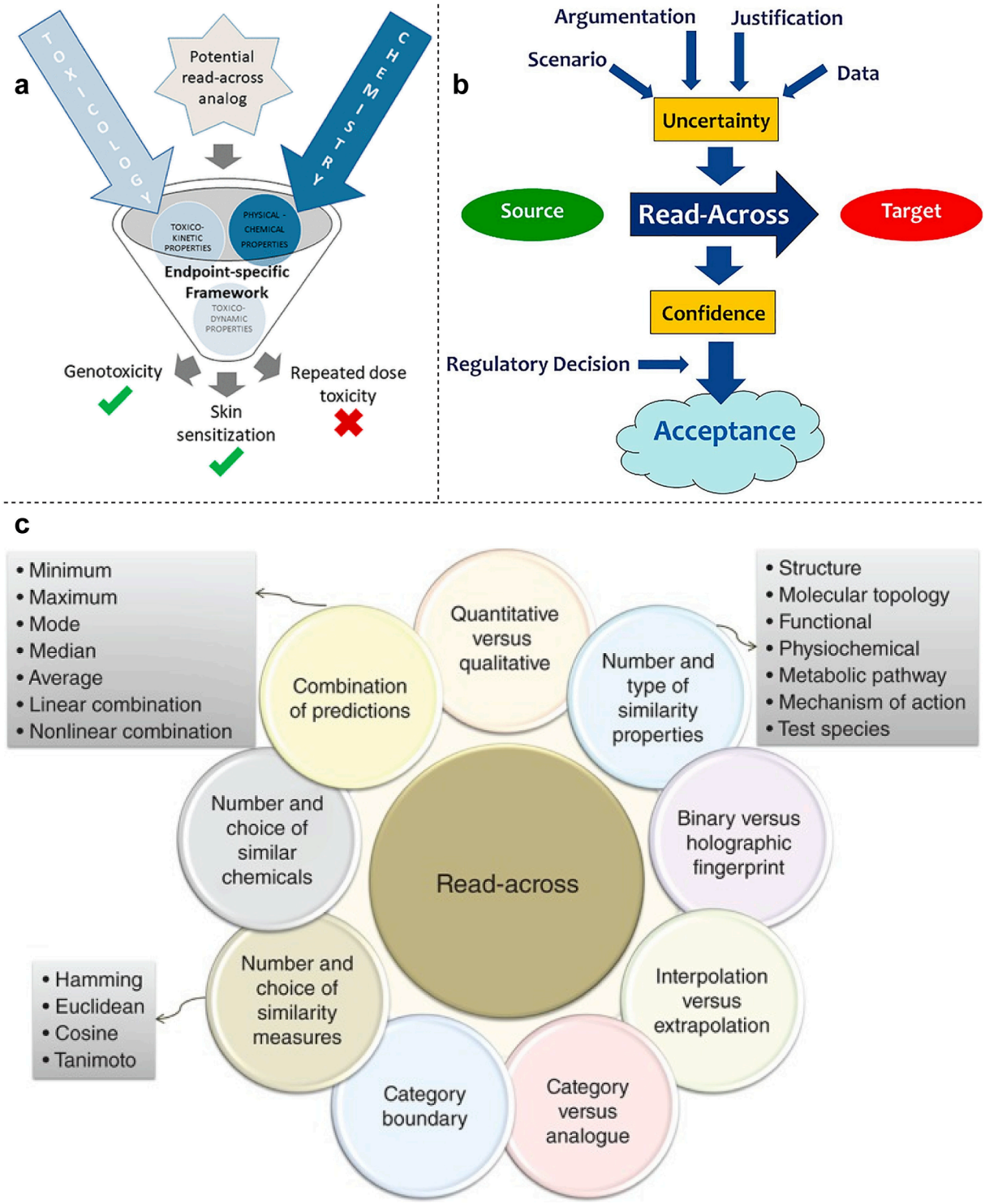

Fig. 7. Read-across prediction and properties. (a) End point-specific framework for read-across analog selection (Image adapted from [96]) (b) a structural way of assessment of uncertainty and acceptance in read-across prediction (Image adapted from [108]) (c) different properties of read across models (Image adapted from [49]).

structurally similar materials can be found and used as data sources to assess a target chemical's safety. The quality of the read-across data, the hypothesis and justification of the toxicokinetic and toxicodynamic bases of the prediction, and the pertinent supporting data and information all contribute to the uncertainties of a toxicological read-across prediction (Fig. 7). By identifying and minimizing the uncertainties related to these factors, one can increase confidence in a read-across prediction. As the mode of action for each end point varies greatly, read-across frameworks are more likely to be accepted when applied end point-by-end point[96]. These advancements will aid in the development of read-across case studies as well as nanosafety assessments in future (Fig. 7).

6. Role of molecular dynamics simulations in toxicity-based investigations: advances and applications

Nanoinformatics begins with the application of modeling and simulation approaches toward an array of objectives, such as integrating together toxicological data into clinical and personal databases or establishing novel strategies for scientific ontologies[97]. The method used to analyze the time-dependent behavior of a molecular system is known as molecular dynamics (MD) simulation, and it is an arising technology in computational nanotoxicology. The molecular system refers to the physical motions of atoms and molecules in the system. MD simulations could provide comprehensive details on the molecule's fluctuations and structural alterations. To investigate the potential hazards of nanomaterials in nanotoxicology, many computational algorithms for molecular dynamic simulations have been built[98]. Scientists are interested in exploring the interactions among nanometers and tiny-range nanoparticles and biological molecules using different MD simulations[99].As was already noted, in a molecular system, MD simulation is the time-dependent modeling of atomic movements that are governed by interactions between atoms within a defined radius. The dynamic operations and statistical characteristics of a molecular system can be monitored and thoroughly investigated by documenting and analyzing the coordinates, velocities, and forces of the individual particles inside it[100]. In the disciplines of structural biology, drug development, toxicology, and nanotechnology, several MD simulation methods, and algorithms such as Molecular mechanics, Quantum mechanics, ab initio, hybrid Quantum, and Molecular mechanics have been built and are often utilized[101102]. Molecular dynamic simulation follows a standard protocol for an accurate biological macromolecule and nanoparticle. Aqueous media at least partially contains the majority of biomolecules. Prior to performing MD simulations, it is standard practice to place a biomolecule in pure or ion-containing water. The majority of MD simulations use various water models to do precise solvent computations of biological macromolecules. Based on their physiochemical characteristics, the water models employed MD simulations that are depicted by all-atom force fields may be divided into numerous categories. Simple point charge (SPC), SPC/E, transferable intermolecular potential (TIP3P), TIP4P, and TIP5P are the most often utilized water models out of the 46 different water models that are applied in MD simulations[103]. Depending on the number of sessions they need, the level of precision, and other parameters, users may choose the water models to employ in their MD simulations. The SPC model[104], SPC/E model[105], TIP3P model[106], TIP4P model [106], and TIP5P model[107] are among the most often used explicit water models in MD simulations.

Efficient MD simulations depend on having a suitable energy function to describe how molecules interact inside a molecular system in simulation. Typically, parametrized terms derived from experiments or computations using quantum mechanics are included in the energy functions employed in MD simulations. Large macromolecules like proteins are thought to be compatible with parametrized terms. A force field is a collection of energy functions and the parametric variables that correspond with them[109]. In the 1960s, while MM approaches were being developed, the force field idea was first proposed. In general, force fields are cumulative. Class II force fields are those that contain higher-order terms and are not additive. Predicting molecular structures, vibration spectra, and enthalpies of isolated molecules is the main objective of force fields. For the modeling of diverse biological a variety of force fields have been created and employed[110]. The most widely used programmes for MD simulations are AMBER[111], AMOEBA[112], CHARMM[113], GROMAS[114], OPLS[115], and ReaxFF[116]. MD simulations depend on molecular system preparation. A starting system with atomic conflicts may break the MD simulation's tertiary structure, terminating it. To avoid a poor initiating system, apply solid preparatory practices. MD simulations start with a 3D structure from investigations like crystallography and NMR spectroscopy, homology modelling, docking simulation, or an MD trajectory. Conjugate-gradient and steepest-descent methods are used to optimize the structure's atomic coordinates by minimizing the original structure's potential energy.

Before MD simulation, an explicit water model must solvate the minimized structure. First, a periodic box with 8–12 Å surfaces is placed around the minimized structure. In explicit models, water molecules fill the periodic box. MD simulation on water molecules for 1–5 ps smooths the water network[117]. Finally, the biomolecules, fluids, and molecular systems are optimized for MD simulation. One such strategy that has been successful at the fundamental level is nanoparticle-mediated medication delivery. By analyzing the interactions between proteins and nanoparticles, it has become possible to better understand how nanoparticles affect the human body. Using all-atom molecular dynamics simulations (MDS), Hazarika *et al.*, assessed the effect of silver nanoparticles on the structure and function of human serum albumin [118]. Being a transport protein, HSA may not function properly if its structure changes. The results of the post-MD analysis demonstrated that the nanoparticle and human serum albumin interact and that the conjugated system stabilized over the course of time. The study indicated that the AgNP interacts with HSA without changing its secondary and tertiary structures, which in turn does not alter the protein's ability to function (Fig. 8. a & b). Because silver nanoparticle has no negative impact on serum proteins, it is advised to use them in the transportation of conjugated medicinal molecules. Because human serum albumin is found in the circulatory system, it may be possible to use silver nanoparticles in a variety of biological applications further stated by the authors[118]. In another study to investigate the gold nanoparticle and corona formation, *Sajib et al.*, studied ovispirin-1 and lysozyme corona formation on the bared surface of the nanoparticle using coarse-grain simulation for the purpose of drug delivery (Fig. 8. c, d, & e). Several factors, including protein-surface interactions, protein–protein interactions, and the hydrophobic effect of the surface, were shown to control protein corona formation. It has been determined that the size of the nanoparticles and the nature of the protein affect the corona structure. In contrast to the inhomogeneous multilayered aggregates formed by lysozyme on gold NP surfaces, ovispirin proteins form homogeneous single-layered adsorption.

Increased angular degrees of freedom for protein adsorption orientation occurs because of the reduction in nanoparticle size. [119]. Although studies have successfully shown the importance of molecular dynamics simulations in, future investigations related to so may assist its further advancement and applications for the prediction of toxicity of materials.

7. A glance at biofunctionalized nanoparticles and the inclusion of computational approaches towards their cytotoxicity analysis

Biofunctionalization is a crucial element in the process of synthesizing innovative materials. It comprises the alteration of the physicochemical characteristics of a material's surface, enabling a diverse range of applications. These applications include the use of the material as an implant, prosthesis, or topical/oral additive. The principal goal of biofunctionalization is to improve the organism's biological response to the

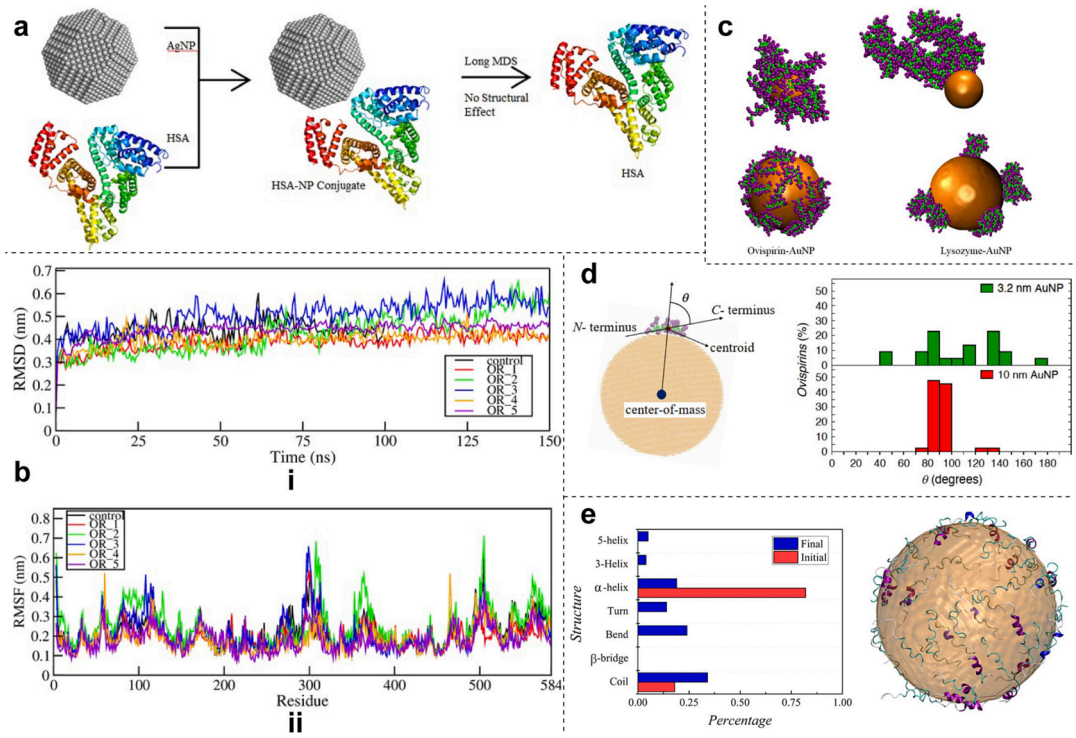

Fig. 8. Molecular dynamic simulation of nanoparticle and protein interaction. (a) Silver nanoparticle and human serum albumin interaction and (b) Root-mean-square deviations (RMSD) and root-mean-square fluctuations (RMSF) plots on silver nanoparticle and human serum albumin interaction. (Image 5. a and 5. b adapted from [118]). (c) Ovispirin and lysozyme corona formation on gold nanoparticles with size 3.2 nm (upper, small sized particles) and 10 nm (Lower, bigger size). Ovispirin protein orientation distribution profile with regard to the surface of gold nanoparticle, (d) adsorption of protein at orientation angle θ, and (e) distribution of θ for proteins on 3.2 and 10 nm gold nanoparticle surfaces. (adapted from [119]).

engineered material[120]. Studies have demonstrated the bio-functionalized nanoparticles has also been shown a promising agent for the therapeutic delivery platforms. The study used MD simulation and calculations based on density functional theory to shed light on the mechanisms involved in the creation of nanoparticles and the method by which free medicines are released from methotrexate-camptothecin nanoparticles[121]. The hydrophobic and hydrogen bonding interactions between methotrexate-camptothecin prodrug molecules and water molecules allowed prodrug monomers to self-arrange into a spherical shape, which was followed by the formation of self-assembled nanoparticles, according to the moment of inertia calculated using the MD simulation.The computational simulation also showed that the release of methotrexate and camptothecin-free medication in an acidic environment was made possible by the breaking of the methotrexate-camptothecin ester link. Prodrug-based nanoformulation may therefore be a potential strategy for a regulated, targeted drug delivery system, according to the experimental and computational results[122].

Two coarse-grained methodologies, notably dissipative particle dynamics (DPD) and coarse-grained molecular dynamics (CG MD) employing the MARTINI force field, have been employed in the study of drug-excipient interactions[123]. The DPD simulations represent excipient molecules as discrete beads, facilitating the prediction of drug-polymer interactions and the polymer's efficacy in encapsulating hydrophobic pharmaceuticals such as prednisolone and paracetamol. However, the simulations proved to be inadequate in accurately representing the interactions between polymers and hydrophilic medicines, such as isoniazid. This suggests that the simulations did not successfully capture the dynamics of hydrophilic drug-polymer interactions. CG MD (the MARTINI force field) is an efficient model for simulating polymer self-assembly in micelles and drug distribution within the micelle[124]. By using DPD simulation, the self-assembly mechanism was broken down into two steps[123]. The first step described how chains of polyethylene glycol cetyl ether (PEGCE) arranged themselves to form the core of the nanoparticle in the presence of cyclohexane solvent (a hydrophobic environment), and the second step described how the prodrug molecule assembled itself around the PEGCE core. The projected nanoparticle size agreed well with the actual experimental findings according to simulation results[125]. Additional research could clarify the function of computer simulations in the cytotoxicity evaluation of bio-functionalized nanomaterials.

8. Application of computational tools for nanostructures modified by antimicrobial peptides and monoclonal antibodies

Proteins and peptides can be changed to some extent to change their biological functions and pharmacological activities, but their 3D structure and surface properties are essential for interactions with receptors or ligands[126]. An essential tool is the use of molecular dynamics (MD) simulations on antimicrobial peptides and monoclonal antibodies modified nanostructures. Studies on drug design have made substantial use of the effective prediction of the folding and dynamics of a number of proteins and peptides using MD simulations[126127]. The halogen bond (or X-bond) is an exciting tool for engineering protein–ligand interactions. Recently, the force field has been simplified by confining the number of variables to just one for each type of halogen and by estimating the electrostatic variable using a conventional calculation of atomic charges for the constrained electrostatic potential. Glycoproteins, often referred to as therapeutic monoclonal antibodies, are essential components of the immune response because they precisely recognize and bind to certain antigens, such as bacteria or viruses, and contribute to their destruction. There is a need for the development of tools that would enable a quick and correct interpretation of glycoproteomics data due to the time-consuming and laborious interpretation of mass spectrometry (MS) output data linked to glycan structure and glycosylation site identification. Although there is already commercial software for glycoproteomics analysis, such as SimGlycan® (SCIEX),

MassyLynxTM (Waters), and BionycTM (Protein Metrics), highly competitive and reliable open-source software is still being developed because manual data validation is still necessary because the majority of commercial tools have high false discovery rates [128]. Future studies assisted with the mentioned computational tools and softwares may discover the detailed properties of the the nanostructures modified with antimicrobial peptides and monoclonal antibodies.

9. Conclusion

In order to produce new products for widespread safe use in electronics, cosmetics, optical devices, etc., it is crucial to assess the toxicological impacts of novel nanomaterials. The use of these materials, in particular, has grown significantly, despite the fact that there is still debate over their toxicity and that numerous international organizations are working to establish and standardize procedures for evaluating and managing their potentially dangerous effects. Characterization of nanoparticles is one of the utmost importance measures for revealing the connections between nanostructure and biological processes as well as for accelerating the calculation of tailored NMs. On the contrary, the time and money needed to accomplish a thorough experimental review would be considerable, taking many years. To process experimental data further for a prediction model, standard computation models are required. These models gather experimental data and transform it into standard formats. The quantity and quality of the data that is available play a significant role in the development of computational approaches like molecular docking or molecular dynamics simulations and models like nano-QSARs. Although enormous efforts have been invested in data standardization and curation over the past few years, the information accessible for nanoparticles is relatively limited in comparison to that for bulk chemicals and small molecules. As a result, the applicability area of current hazard models for nanoparticles is restricted, which limits their use in regulatory risk assessment. By creating new high-throughput and high-content screening technologies for the quick characterization of vast nanoparticle libraries at various exposure circumstances, the current data shortage could be overcome. It is necessary to standardize experimental tests in terms of future approaches for the assessment of toxicity. This standardization must be used in juxtaposition with computational and experimental approaches to help researchers better understand risk assessment and other problems in the future. Future generations of fundamental tools for implementing intelligent testing strategies for and supporting the estimation of the toxicity risk assessment of nanoparticles and regulatory decision-making will be made possible by the use of *in silico* methods and sophisticated machine learning techniques to obtain NP descriptors.

10. Current challenges and future perspectives

The evolution of nanoscience from benchtop science to applied technology during last few years, has made it crucial to assess its related toxicity for usage in several commercial products. Data scarcity in nanotoxicology substantially restrains the creation of relevant and reliable *in silico* models. Additionally, it is well known that machine learning algorithms perform better on bigger datasets. There is disagreement over the amount of information needed to develop trustworthy *in silico* models, but findings show that building models from the data on toxicity that is currently accessible can result in strong models with good predictive power. In order to ensure accurate and efficient application of *in silico* models, it is essential to (1) comprehend the methods' advantages, disadvantages, range of use, and interpretation; (2) select the most suitable method for the issue at hand; and (3) tailor these methods for each issue as needed. With the use of deep learning and AI-based technologies that will more precisely be able to provide an integrated view on NP design, this might be feasible in the future. Interoperable and effective procedures are needed to fully utilize research data from bioscience groups, and as they aid in the development of an open data sharing culture. The application of data mining methods in the study of nanotoxicity, to run the trial data programmatically and foresee the toxicity of nanomaterials. It is hard to tell how close we are to achieving this goal. However, recent advancements in both nanomedicine and computational tools have greatly accelerated efforts toward achieving this pivotal goal.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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