

A Brief Review on the Exploration of Nanocomposites and Their Properties Through Computational Methods for Biological Activity Evaluation [†]

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Abstract

This brief review examines the application of various computational approaches to investigate the physicochemical and interfacial properties of nanocomposite systems. Density functional theory (DFT), a quantum-mechanical technique, examines the fundamental properties of nanomaterials. Molecular docking studies have also been explored to show how different biological macromolecules can interact and bind with the nanoparticles (NPs') surface, along with the molecular dynamics (MDs) simulations, which further strengthen the docking findings. Furthermore, nanotoxicology, a comparatively less explored field, has also been introduced, providing an insight into the interactions between nanomaterials and the environment and biological systems, including the harmful consequences.

Keywords: nanocomposites; computational tools; environment; biological activity; molecular docking; health

1. Introduction

Nanocomposites are made of a host (or matrix) material, such as ceramic, metal, or polymer, reinforced with nanoscale fillers, like NPs, nanotubes, nanosheets, or nanoclays [1]. When compared to traditional composites, the addition of nanoscale building blocks can often result in improved or unique properties, such as increased strength-to-weight ratios, enhanced electrical or thermal conductivity, improved barrier qualities, and multifunctionality (e.g., sensing, catalytic, and thermal management). Synthesis and characterization have previously accounted for an extensive amount of nanocomposites research. This includes optimizing filler dispersion, interfacial bonding, processing methods, and post-treatment, followed by measurements of macroscopic properties (mechanical tests, thermal/electrical conductivity, and microscopy) [2]. In order to link filler content, morphology, and alignment to composite behaviour, empirical or semi-empirical models and micromechanics theories (such as rule-of-mixtures, Halpin–Tsai equations, and percolation models) have also been employed [3]. However, the experimental methods are time-consuming and costly to explore the high-dimensional space of filler varieties, sizes, forms, concentrations, surface chemistries, and processing conditions. It is challenging to methodically understand how morphology, molecular-level interactions, and nanoscale interfacial phenomena affect macroscopic performance. These difficulties lead to a rising trend in nanocomposite research toward computational and in silico methods [4]. There



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are unique benefits of using computational techniques while exploring nanomaterials and nanocomposites. They provide understanding about the interactions at the atomic and molecular scale that direct dispersion, interfacial adhesion, stress transfer, thermal transport, and failure mechanisms [5]. They make it possible to predict properties before synthesis, optimize design parameters, screen material combinations virtually, and couple them with experiments in a feedback loop. Moreover, multiscale modelling frameworks can amalgamate many regimes by bridging the gap between the atomic scale and mesoscale and continuous behaviour [6]. These days, a wide range of computational tools is employed to study and synthesize nanocomposites for various applications and scales. Among the most widespread techniques are MD simulations, providing an atomistic understanding of the filler–matrix interface’s interfacial structure, dispersion behaviour, stress transfer mechanisms, and thermal transport [4]. Understanding the photocatalytic, electrical, and sensing behaviour of nanocomposites requires an understanding of electronic structures, charge transfer, adsorption energies, and defect energetics, all of which could potentially be studied using quantum mechanical and *ab initio* techniques, especially density functional theory (DFT) [7]. Coarse-grained and mesoscale simulations, like finite element modelling (FEM) and dissipative particle dynamics (DPDs), are used at larger sizes for evaluating the mechanical, thermal, and viscoelastic responses of nanocomposites outside of the atomistic regime [5]. Phase behaviour, morphological evolution, and thermodynamic equilibria in polymeric or hybrid systems are being studied using Monte Carlo simulations [8]. Molecular docking and molecular simulation techniques have become successful approaches for examining interactions between nanocomposite surfaces and biomolecules like proteins, DNA, and cell membranes in the context of biomedical and environmental nanocomposites. These techniques offer predictive insights into nanotoxicology and biocompatibility [9]. By combining quantitative structure–activity relationship (QSAR) modelling, DFT-based reactivity assessments, and molecular modelling, computational nanotoxicology predicts toxicological responses without needing a lot of *in vivo* testing, promoting safer-by-design principles [10]. Also, the promotion of artificial intelligence (AI) and machine learning (ML) has accelerated data mining, virtual screening, and property prediction of nanocomposite systems, allowing researchers to discover complex structure–property relationships that were previously unattainable using conventional techniques [5]. From atomic-level mechanisms to macroscopic property prediction, these techniques collectively provide a comprehensive computational environment for nanocomposite research, which facilitates experimental investigations and steers the development of sensible materials. The goal of this brief review is to present a short yet thorough overview of current initiatives that use computational methods to comprehend, develop, and optimize nanocomposites. The article can be useful for researchers studying material science and nanomedicine to determine how computational strategies can help predict the properties of nanocomposites, particularly for their applications in biological activity evaluation. A few of the strategies, like molecular docking, DFT and computational nanotoxicology, have been explored with the help of recent studies.

2. Molecular Docking Studies

To predict the optimal orientation and binding affinity of small molecules to macromolecular targets (proteins, nucleic acids), a computational technique known as molecular docking was initially created. Docking and related molecular-level simulations have been optimized for use in nanocomposites to investigate nano-bio and nanomolecule interactions. These simulations are capable of predicting the interactions of NP surfaces, surface-functionalized moieties, polymer segments, or composite ligands with biological macromolecules (enzymes, membrane proteins) and small molecules (drugs, pollu-

tants) [11,12]. This data is helpful for several nanocomposite research topics, including the reasonable creation of antibacterial and drug-delivery NPs [13,14], determining probable adsorption/adsorbate configurations for sensing or catalysis [15], screening for possible nanotoxicity by using biomolecular targets that are likely to bind [11], and providing guidance for surface-functionalization techniques to enhance biocompatibility or selectivity [13]. Docking creates an effective in silico screening funnel that lowers experimental burden and expedites hypothesis-driven synthesis of functional nanocomposites when paired with complementary approaches (MA for dynamic behaviour, DFT for electronic/chemical detail, and experimental tests). Graphene oxide (GO) (2% and 4%) and a predetermined quantity of polyvinylpyrrolidone (PVP)-doped MoO_3 nanostructures (GO/PVP-doped MoO_3) were synthesized in a study by Ikram M. et al. [16]. Evidential molecular docking analyses were performed to determine their catalytic and antibacterial efficacy. When employed against *Escherichia coli* (*E. coli*), the produced nanocomposite proved to be an efficient antibacterial agent. Compared to ciprofloxacin, 4% GO/PVP-doped MoO_3 showed good bactericidal efficacy against *E. coli* at greater doses. Flexible MD simulations were analyzed using the Surflex–Dock module of the molecular modelling software package SYBYL-X 2.0 to investigate the binding interactions of nanostructures with the active site residues of the chosen proteins. Additionally, the potential inhibitory effect of the produced nanocomposites on dihydrofolate reductase and enoyl-[acyl carrier protein] reductase was also investigated, and was found to play a role in the synthesis of fatty acids and folate, respectively. The ideally docked conformation of PVP/ MoO_3 within the active domain of FabI *E. coli* revealed an H-bond with Ile20, Ala21, Ser41, Lys163, and Thr194. A 3D image of a binding pocket inside the FabI binding site is displayed in Figure 1. Thus, the produced nanostructures inhibited *E. coli* quite well.

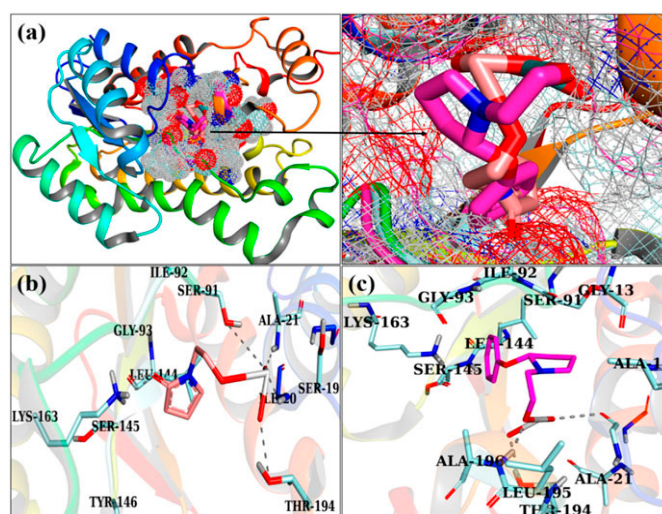


Figure 1. Three-dimensional view of a binding pocket (a) and the binding interaction pattern of PVP/ MoO_3 (b) and GO/PVP/ MoO_3 (c) inside the binding site of FabI [16].

Recently, silver nanocomposites containing mono- and bis-thioureidophosphonate (MTP and BTP) were synthesized, and docking experiments were conducted in addition to antibacterial and antibiofilm investigations. With the help of Discovery Studio, molecular docking investigations were carried out using the molecular operating environment (MOE). The protein data bank included four proteins (PDB codes: 4DKI, 2FQT, 5ZHN, and 3ZQE) from several Gram-positive and Gram-negative bacteria that were downloaded for modelling purposes. In addition to the enhanced binding energy of MTP/Ag NC by 37.8% toward the *B. subtilis*-2FQT protein, the molecular docking assessments confirmed the superior binding affinity of BTP over MTP [17]. In a similar vein, a work by Riaz S. et al.

shows how to systematically add varying quantities of GO via a co-precipitation technique to a given quantity of polyacrylic acid (PAA)-doped SnO₂ QDs to create GO/PAA-SnO₂ nanocomposites. Numerous characterization and application experiments were conducted in addition to molecular docking research. The ability of the nanocomposites, SnO₂, PAA-SnO₂, and GO/PAA-SnO₂, to bind was evaluated against enzymes that are necessary for bacterial development, particularly those involved in the creation of cell walls and nucleic acids, such as DNA gyrase and beta-lactamase. ICM Molsoft software was used for molecular docking calculations. The protein data library provided the 3D structural coordinates of the enzymes that were chosen as potential targets. DNA gyrase and beta-lactamase were identified by PDB IDs 5MMN (Res: 1.9 Å) and 4KZ9 (Res: 1.7 Å), respectively. Additionally, the supplied nanocomposites—SnO₂, PAA-SnO₂, and GO/PAA-SnO₂—were anticipated by molecular docking studies to be possible inhibitors of DNA gyrase and beta-lactamase *E. coli*. Figure 2 displays a three-dimensional representation of the binding relationship between nanocomposites and beta-lactamase *E. coli* active sites [18].

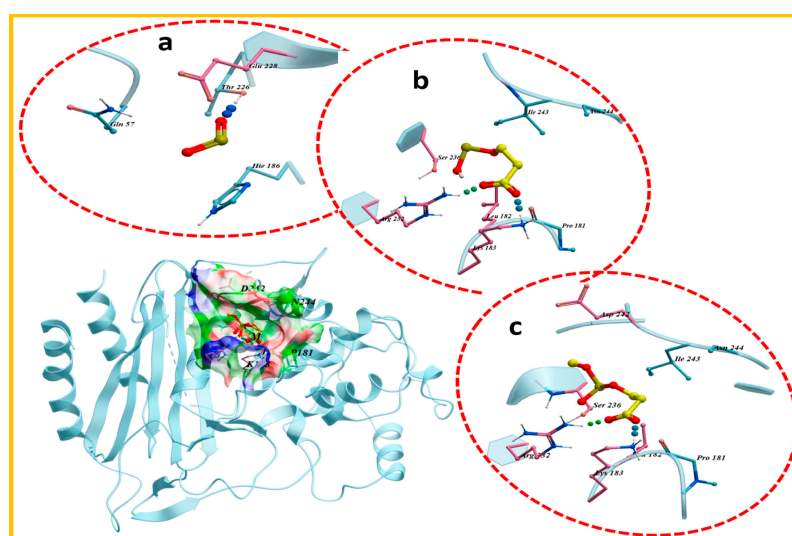


Figure 2. Three-dimensional view of binding interaction of nanocomposites within active sites of beta-lactamase *E. coli* (a) SnO₂, (b) PAA-SnO₂, and (c) GO/PAA-SnO₂ [18].

Abada et al. described bio-designing CuO@ZnO nanocomposites utilizing wasted mushroom substrate (SMS) in another relatively recent study. The activity of CuO and ZnO NPs was compared to the crystal structure of *C. albicans* proteins using molecular docking, which was simulated using the Molecular Orbital Environment (MOE) program. Three-dimensional structures of the main target receptors, with codes 4YDE, 3DRA, and 1EAG, were obtained from the Protein Data Bank (PDB) to determine the inhibitory potential of the investigated compounds. Common hydrogen bonds and strong binding affinities were revealed by the molecular docking experiments. The 4YDE, 3DRA, and 1EAG proteins of *Candida albicans* were found to have optimal binding sites for the NPs, with binding affinities of interactions of -2.7942 , -3.30097 , and -2.52129 kcal/mol and -3.78244 , -4.6029 , and -4.1352 kcal/mol, respectively. According to the results, the CuO@ZnO nanocomposite may successfully inhibit the growth of *C. albicans* [19]. Similarly, a different study by Sagkan I. R. et al. documented the impact of the silver-graphene oxide-cobalt oxide nanocomposite on the cytotoxic levels in HepG2 and MRC-5 cell lines, as well as molecular docking studies. AutoDock Vina 1.2.3 (the latest version) was utilized to perform molecular-scale docking simulations. Therefore, the binding conformations and binding free energy (ΔG) values of nanomaterials resulting from the interactions of GO-Co₃O₄ nanocomposite, Ag-GO-Co₃O₄ nanocomposite complexes, and Co₃O₄ NP against the B-DNA dodecamer, the crystal

structure of a high-resolution DNA conformation, were calculated. The nanomaterials demonstrated DNA recognition by minor groove binding, with molecular affinities ranging from -4.82 to -11.66 kcal/mol, according to molecular docking investigations [20]. Some docking studies reported to include nanocomposites are mentioned in Table 1.

Table 1. Some docking studies involving different nanocomposites.

S. No.	Nanomaterial	Target Protein	Role of Protein	Software Used	Major Findings	Reference
1	Boron-doped reduced graphene oxide	Bovine Serum Albumin (BSA)	Transport and binding of molecules	AutoDock Vina 4.2	Revealed strong binding affinity, suggesting potential for drug delivery applications.	[21]
2	CeO ₂ -GO	Superoxide Dismutase 1 (SOD1)	Reactive oxygen species detoxification	AutoDock Vina v1.2.x	Showed interaction with both mutated and non-mutated forms, suggesting therapeutic potential.	[22]
3	Zn-MnO	Methicillin-resistant Staphylococcus aureus (MRSA) enzymes	Antibiotic resistance mechanisms	Molecular Orbital Environment (MOE)	Revealed binding interactions with multiple MRSA enzymes, suggesting antimicrobial activity.	[23]
4	Fe-Zn-TiO ₂	DIPA and bacterial proteins (<i>E. coli</i> , <i>S. aureus</i>)	Photocatalytic degradation and binding	AutoDock Vina	Exhibited effective degradation of pollutants and strong binding to bacterial proteins.	[24]
5	Fe ₃ S ₄ /TiO ₂	Quinalphos pesticide and fish health proteins	Binding and degradation	AutoDock Vina	Identified effective binding sites for pesticide degradation and potential impact on fish health.	[25]

3. DFT Studies

DFT is a quantum mechanical technique that balances accuracy and computational cost for atomic systems by computing electronic structure based on electron density rather than wavefunctions. DFT is particularly useful for examining fundamental properties such as band structure, density of states (DOSs), charge transfer, defect energetics, interfacial bonding, and surface reactivity in nanocomposite research. These understandings aid in the prediction and explanation of how the combination of various nanoscale phases (such as metals, oxides, 2D materials, and polymers) affects the behaviours of optical, electrical, catalytic, and energy storage processes. DFT, for instance, can show how doping, hetero-interfaces, or nanofiller decorating improve charge transport across filler/matrix boundaries, lowering band gaps [26]. By assessing adsorption energies or interaction strengths with tiny compounds or biomolecules, it can also help with stability and toxicity screening. DFT assists in validating ideas and directing the logical design of nanocomposites with optimal properties when combined with tests (optical measurements, electrochemical testing, and microscopy) or other computational techniques (MDs and docking). Using DFT simulations in carbon-doped TiO₂ nanocomposites, a recent work explores the impact of C element doping on the CO₂ adsorption ability of TiO₂. Using the CASTEP and DMol3 modules, all of the computational simulations were carried out inside the Materials Studio framework to investigate a variety of titanium dioxide surface models. Investigating the structural and electrical characteristics of TiO₂ surfaces under several

circumstances was the goal of these simulations. $\text{TiO}_2\text{-2C}$ and $\text{TiO}_2\text{-3C}$, which represent the two carbon doping concentrations of 4% and 6%, respectively, were taken into consideration. According to the results, the band gaps of $\text{TiO}_2\text{-2C}$ and $\text{TiO}_2\text{-3C}$ became lower than the band gap of pure TiO_2 following carbon doping. This shows that the electrical structure of TiO_2 was effectively improved. Calculations of barrier energy also showed that $\text{TiO}_2\text{-2C}$ and $\text{TiO}_2\text{-3C}$ had a lower energy barrier than pure TiO_2 , which made the transition to $^*\text{COOH}$ intermediates easier. These results offer important knowledge about the electrical structural alterations brought about by carbon doping in TiO_2 , which can help build environmentally friendly and sustainable energy solutions to the world's climate problems [7].

In a different work, the researchers created MoS_2 nanoflowers (MoS_2/CuO) adorned with CuO NPs using a straightforward hydrothermal method. The impact of CuO concentrations of 0, 1, 2, 4, and 6 wt% on the composite nanomaterials' surface morphology and their structural, optical, and electrochemical characteristics was investigated. The impact of CuO NPs on the electrical and optical characteristics, as well as the electrochemical performance of the nanocomposite, was theoretically understood using density functional theory. The Vienna ab initio simulation tool (VASP) was employed to perform the first application of DFT calculations. The projector augmented wave (PAW) technique, which takes into account the interaction between valence electrons and core ions, was used in this investigation. According to theoretical predictions, CuO increases the active surface area of MoS_2 by preventing its layers from restacking. Greater conductivity, specific capacitance, and a smaller optical band gap are the results of hybridization in the interface region between Mo and O orbitals, which boosts states close to the Fermi level. Longer charging and discharging durations and improved electrochemical performance are the results of the charge transfer from MoS_2 to CuO , which produces a high intrinsic electric field that enhances electron transfer [26].

Similar to this, Adekoya O. C. et al. used DFT to evaluate the potential application of a graphene oxide-based poly(ethylene glycol) (GO/PEG) nanocomposite as a drug delivery substrate for the antibiotic cephalexin (CEX), which is used to treat wound infections. By establishing a hydrogen bond between the oxygen atom on PEG's hydroxyl group and the hydrogen atom on the carboxylic group on GO, the most stable configuration shows how PEG and GO interact. Similarly, after identifying the ideal and thermodynamically favourable configuration, the adsorption energies are calculated. In the most stable drug-exipient system, a hydrogen atom from the carboxylic group of the GO/PEG nanocomposite bonds with a nitrogen atom from the drug's amine group. In moist conditions, drug release for tissue regeneration at the anticipated target cell occurs more quickly than in the gas phase. The total amount of the projected solvation energy indicates how soluble the proposed medication is in the aqueous medium around the open wound. The results theoretically support the possibility of using a GO/PEG nanocomposite as a drug carrier for the CEX medication's prolonged release in wound therapy applications [27].

In a recent study, Abdelghany A. M. et al. used a straightforward casting technique to create chitosan/polyvinyl pyrrolidone/zinc sulfide (CS/PVP/ZnS) nanocomposites. The molecular structures of the PVP and chitosan monomer units were modelled using DFT calculations, which were also utilized for studying the likely interaction geometries between PVP and chitosan (various binding modes) and the possibility of coordination through O or N of the ZnS dopant with the PVP/CS blend. To support patterns observed in UV-Vis optical measurements, the DFT results were utilized to compute electronic characteristics (HOMO–LUMO energies/ ΔE) and theoretical IR (vibrational) spectra for each model, which were then compared with the experimental FT-IR data. The comparison showed better agreement when PVP and chitosan interacted via the NH group. The computed FT-IR spectra from the monomer and complex models replicated the primary experimental bands with minor changes. The observed shifts in FT-IR bands on

ZnS doping are consistent with DFT's suggestion that coordination/complexation occurs preferentially through the polymer blend's oxygen atom (as opposed to nitrogen) for the ZnS-containing models. The model systems' HOMO–LUMO computations (ΔE) revealed variations in line with the empirically reported decrease in optical band gap with increasing ZnS concentration. The interpretation of UV-Vis data was supported by these electronic structure findings. As a result, the DFT work supported the anticipated interaction mechanisms at the molecular level and aided in connecting spectroscopic shifts to structural and electrical modifications in the nanocomposite [28]. Similarly, Adedoya Et Al.'s study used DFT (Via CASTEP in Materials Studio) to explore graphene–polypyrrole (G/PPy) nanocomposites as potential Zn-ion battery electrode materials. The authors calculated the adsorption heights and energies for Zn adatoms on G/PPy and PPy on graphene using DFT. Additionally, they evaluated the theoretical specific capacity and the Zn diffusion barrier on the surface of the nanocomposite. PPy adsorption onto graphene with -1.68 eV at 3.28 Å, weak Zn adsorption (≈ -0.078 eV), a low Zn diffusion barrier (~ 12 meV), and a high theoretical capacity (~ 510 mAh/g) represent a few of the important findings. These computational findings suggest that G/PPy nanocomposites combine favourable capacity, structural stability, and strong ion mobility to provide outstanding performance in Zn-ion batteries [29]. Some DFT studies reported to involve nanocomposites are mentioned in Table 2.

Table 2. Some DFT studies involving nanocomposites.

S. No.	Nanocomposite	DFT Method/ Software Used	Parameters Calculated	Major Findings	Reference
1	Polyaniline/ZnO	B3LYP functional and 6–311G (d,p) basis set	Band gap, HOMO-LUMO	Favourable band alignment and charge transfer capability in the composite, correlating with experimentally enhanced dye reduction	[30]
2	TiO ₂ /WSe ₂	Quantum ESPRESSO software package	Adsorption energy, charge transfer, DOS, band structure, and charge density difference	O ₃ molecules exhibit strong chemisorption on the TiO ₂ /WSe ₂ interface with significant charge transfer, leading to noticeable modulation in electronic properties, suggesting the nanocomposite's high potential as an efficient gas-sensing material for ozone detection	[31]
3	Carbon quantum dots-TiO ₂	B3LYP functional and 6–311G (d,p) basis set	Adsorption energy, electronic density, band structure changes, charge separation	Decorating TiO ₂ with an optimal amount (~ 0.5 wt%) of CQDs yields enhanced photodegradation of aromatic VOCs (64% vs. 44% for bare TiO ₂), attributed to better light absorption, stronger adsorption of VOC molecules, and improved electron–hole separation mediated by the newly introduced interface states	[32]

Table 2. Cont.

S. No.	Nanocomposite	DFT Method/ Software Used	Parameters Calculated	Major Findings	Reference
4	(CS/M/S/GO)	Gas-phase and implicit solvation/water medium	Binding (interaction) energies, ionization energies, conformational energies, dipole moments, and frontier orbital (HOMO–LUMO) properties	The modelled nanocomposite shows favourable binding with cisplatin (i.e., strong interaction) and that functionalization enhances the interaction and stability of the drug–carrier complex in both gas and aqueous environments.	[33]
5	Polycarbonate/ TiO ₂ /ZnO	B3LYP functional and 6–311G (d,p) basis set	HOMO–LUMO gap	Incorporation of TiO ₂ and ZnO nanoparticles into the polycarbonate matrix led to a decrease in the optical band gap and increased absorption in the UV-visible region.	[34]

4. Nanotoxicology Studies

Nanotoxicology is the study of the possible harmful consequences of nanocomposites, which has increased in tandem with their growing use in commercial, environmental, and medicinal applications. Nanotoxicology is the study of how nanomaterials interact with the environment and biological systems, including potential negative effects brought on by their composition, size, shape, surface chemistry, and charge [35]. Computational and in silico methods are being used more and more to predict toxicity, clarify molecular mechanisms underlying toxicity, and direct safer-by-design tactics because conventional in vitro and in vivo toxicology assays are time-consuming, costly, and frequently ethically limited [36]. These methods include DFT and molecular dynamics simulations for interaction energies, molecular docking of nanomaterial surfaces or functional groups with protein targets, quantitative nanostructure–activity relationship (nano-QSAR) models, and machine learning or artificial intelligence (AI) tools to integrate enormous quantities of physicochemical properties [10]. Recent research illustrates how computational nanotoxicology can estimate environmental risk, assist regulatory assessment, and identify proteins or pathways that may be impacted by exposure to nanocomposites. For instance, a review by Tang W. et al. explores various modelling and computational frameworks that are being developed or used for risk assessment of engineered nanomaterials (ENM). These can be categorized into two main groups: hazard/effect models and exposure/fate/kinetics models. These include physiologically based toxicokinetic (PBTK) models that model the absorption, distribution, metabolism, and excretion of ENMs within biological systems; multimedia environmental models (MEMs) that predict their distribution and transformation among environmental compartments; and material flow analysis (MFA) models that estimate ENM release, transfer, and predicted environmental concentrations (PECs). Quantitative nanostructure–activity relationship (QNAR) models have been described as useful predictive tools that use statistical or machine learning techniques to correlate ENM physicochemical features with toxicity endpoints. A computational nanotoxicology model-based environmental risk assessment methodology for ENMs is presented in Figure 3 [36].

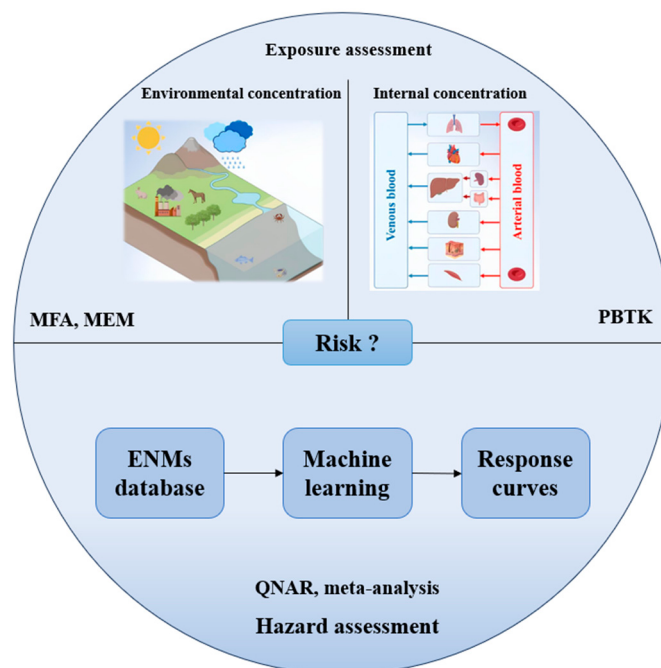


Figure 3. Environmental risk assessment framework for ENMs with computational nanotoxicology models [36].

The effectiveness and initial safety of biogenic zinc oxide NPs (ZPCL) made with watermelon rind extract were examined in a recent work by Akhter et al. The authors evaluated properties like human intestinal absorption, blood–brain-barrier penetration, oral bioavailability, receptor binding (androgen, estrogen, etc.), enzyme inhibition (CYP450 family), P-glycoprotein interactions, and acute oral toxicity to perform *in silico* ADMET predictions. They did this using well-known online tools (AdmetSAR, PROTOX-II). According to their findings, ZPCL was expected to have low acute toxicity with suitable pharmacokinetic profiles *in silico*. Additionally, they proposed potential mechanisms of antibacterial action by analyzing binding affinities between ZnO NPs and microbial proteins using molecular docking. The study's toxicity assessment is still in its early stages, though, as it does not address possible long-term, systemic, or environmental hazardous effects and does not include experimental cytotoxicity or *in vivo* toxicity data. There was a study on physical characterization (size, surface charge, shape), which is significant because these characteristics have a big impact on NP toxicity. When combined, these methods represent helpful first steps in assessing the safety of nanomaterials [37]. By using docking simulations between metal oxide NPs (Al_2O_3 , NiO) and antioxidant enzymes (SOD, CAT, GST), the authors of a different study investigate the possible molecular basis of nanoparticle toxicity. They discover that NiO has a higher binding affinity than AlO_3 in their active sites, particularly for CAT and GST, using docking tools (CB-Dock, AutoDock Vina) and enzyme structures from AlphaFold. It also means that fish may be more susceptible to oxidative stress as a result of NiO NPs' increased inhibition of antioxidant defences. The study reveals how molecular docking can be used as an early warning system in nanotoxicology to determine the inhibitory potential and probable interactions of ENMs prior to *in vivo* testing. To ensure the predictions' biological importance, however, they require experimental validation through exposure studies, oxidative stress indicators, and enzyme activity assays [38]. Similar to this, Mohammadjani et al. used a computational nanotoxicology approach to evaluate the safety and effectiveness of several metal-oxide nanoparticles (MONPs) that have a carbon layer on top. The study compares the binding affinities of these MONPs with those of conventional medications against a variety of

bacterial and cancer protein targets using AutoDock 4.2.6. PROTOX-II predicts LD₅₀ values for each NP in comparison to conventional medicines to evaluate hazardous potential. According to the results, MgO and FeO₃ MONPs frequently attain binding energies that are competitive with pharmaceuticals for certain targets, but they also tend to have lower LD₅₀ values (i.e., a higher risk of toxicity) than conventional medications. This study underlines the crucial compromise in nanomedicine: reducing toxicity while attaining robust target interactions [39]. In a distinct hybrid experimental–computational work, Latif M. et al. synthesize a NiFeO₄/CeO₂/GO nanocomposite for environmental remediation with the dual goals of removing antibiotic contaminants and evaluating the nanocomposite’s antibacterial efficacy. DFT calculations were used to determine the band gaps, adsorption energies, and charge distribution on the composite, offering mechanistic insight into adsorption and photocatalysis. They also paired this with molecular docking to investigate the interactions of tetracycline or its broken fragments with bacterial protein targets. The findings of the docking study of intermediates show whether toxic binding to biological proteins remains; identification of degradation by-products helps to determine whether breakdown results in harmless compounds; antibacterial assays demonstrate the composite’s inherent biological activity; and DFT data on electronic structure tell us how the material might generate reactive species or how stable it is [40,41].

5. Challenges and Future Prospects

Although nanocomposite research has greatly benefited from computational techniques like DFT, molecular docking, and molecular dynamics, each method has inherent limitations. Although DFT offers precise structural details, it is still computationally demanding and limited to entities of a small size [42]. MD simulations describe atomic-level dynamics and interfacial behaviour; however, their accuracy is highly dependent on the quality of force fields and simulation timeframes [43]. Molecular docking provides quick predictions of binding and interaction, but it frequently overlooks solvent effects, entropic contributions, and full biomolecular flexibility [44]. Consequently, predictive models may deviate from experimental outcomes.

Future research should focus on establishing integrated models that incorporate simulation sizes ranging from atoms to bulk materials to obtain more realistic findings. Machine learning and artificial intelligence can help speed up property prediction and material discovery, but they require accurate data and sufficient validation. It is also vital to combine computational findings with experimental data in order to fill the gap between theory and real-world behaviour, particularly for nanocomposites targeted for medicinal and biological applications.

6. Conclusions

Research on nanocomposite materials has evolved, thanks to computational methods. Scientists can finally predict electrical, structural, and biological features with amazing accuracy by combining methods like DFT, molecular docking, molecular dynamics, and Monte Carlo simulations. In addition to providing evidence for experimental findings, these resources provide insight into the stability, molecular-level interactions, and potential toxicological effects of nanomaterials. By using computer simulations to explore nanotoxicology, it is possible to predict undesirable biological consequences early on, reducing the need for lengthy in vivo tests and guaranteeing safer material design. Moreover, the logical design of nanocomposites with distinct characteristics, optimal reactivity, and increased efficiency for environmental and biological applications is made easier by computational studies. Combining computational and experimental methods will be important for accelerating development while cutting costs and time as the need for safe

and sustainable nanomaterials increases. Future studies that incorporate experimental validation and multiscale simulations can provide a better understanding of the behaviour of nanomaterials, facilitating the development of novel, highly effective, and ecologically friendly nanocomposites.

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