MOLECULAR DOCKING STUDY OF PROTEIN-FUNCTIONALIZED CARBON NANOMATERIALS FOR HEAVY METAL DETECTION AND REMOVAL

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Carbon nanomaterials (CNMs) have emerged as highly effective agents for the removal of heavy metals from contaminated water and environments, owing to their unique structural and chemical properties. However, the hydrophobic nature of CNMs and their tendency to aggregate in most solvents present significant challenges to their practical application. Functionalizing carbon-based nanomaterials with proteins offers a promising solution to these issues, potentially leading to systems with unprecedented performance. Before fabricating protein-CNM systems for heavy metal detection and removal, it is crucial to evaluate the metal-binding affinity and potential interaction modes using computational approaches. In this study, a molecular docking technique was employed to investigate the interactions among heavy metal salts (AsO$_4$, Cd(NO$_3$)$_2$, Fe(NO$_3$)$_3$, NiSO$_4$, PbSO$_4$, PtCl$_4$), carbon-based nanomaterials (fullerenes C$_{24}$ and C$_{60}$, and single-walled carbon nanotubes), and β-lactoglobulin. The docking results revealed that: 1) the size, shape, and surface properties of carbon-based materials significantly influence the ability of β-lactoglobulin-CNM complexes to interact with different heavy metals; 2) different heavy metal salts exhibit distinct preferences for the various nanosystems; 3) hydrogen bonding and hydrophobic interactions play a significant role in the complexation of heavy metal salts with β-lactoglobulin-carbon-based materials.
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Detecting and removing heavy metal ions from water is of critical importance due to the severe environmental and health hazards posed by these contaminants [1,2]. Heavy metals such as lead, mercury, cadmium, and arsenic can accumulate in biological systems, causing toxic effects that impact ecosystems and human health. Traditional methods for removing metal ions from water resources, such as solvent extraction [3], ion exchange [4,5], ultrafiltration [6,7], chemical precipitation [8-11], and adsorption [12,13], although beneficial, often have significant limitations. For instance, ion-exchange resins require regeneration with chemical reagents when exhausted, leading to potential secondary pollution [14]. Chemical precipitation is ineffective at low heavy metal concentrations [10,11], while ultrafiltration technology is costly and challenging for large-scale applications [6,7]. Among the various techniques for removing metal ions from aqueous solutions, adsorption is one of the most versatile and widely used methods [12,13]. Numerous low-cost adsorbents, such as activated carbon and carbon nanomaterials, wood char, zeolites, biochar, sawdust, and biopolymers, have proven highly effective in capturing heavy metal ions. Due to their exceptional optical, electrical, chemical, mechanical, and thermal properties, carbon-based nanomaterials are particularly promising for wastewater treatment. Carbon nanomaterials, including carbon nanotubes, fullerenes, graphene, graphene oxide, and activated carbon, have shown a high capacity for adsorbing various heavy metal pollutants [15-25]. For example, carbon nanotubes have demonstrated significant potential for removing heavy metal ions such as lead, cadmium, chromium, copper, and nickel from wastewater, with single-walled carbon nanotubes showing higher absorption capacity compared to multi-walled ones [15-17]. Furthermore, numerous studies indicate that functionalizing or modifying carbon nanotubes enhances their heavy metal adsorption capabilities [18,19]. For instance, Taghavi et al. developed multi-walled carbon nanotubes functionalized with L-cysteine, achieving 89% adsorption efficiency in removing cadmium from water [18]. Similarly, Anitha et al. demonstrated that -COOH functionalized carbon nanotubes exhibit higher adsorption efficiency for Cd^{2+}, Cu^{2+}, Pb^{2+}, and Hg^{2+} than bare single-walled carbon nanotubes [19]. The mechanism by which metal ions are adsorbed onto CNTs is complex and involves several processes, including electrostatic attraction, sorption-precipitation, and chemical interactions between the metal ions and the surface functional groups of the CNTs [15-19].

Graphene is another representative of carbon-based materials, possessing high efficacy for adsorbing heavy metal ions from water. Tabish et al. developed porous graphene as an adsorbent for removing heavy metal ions and other pollutants from water, achieving 80% efficiency in As^{3+} removal, with the material retaining its effectiveness even after regeneration and recycling [20]. Guo et al. created a nanocomposite by partially reducing graphene oxide with Fe$_3$O$_4$ via in situ co-precipitation, resulting in an adsorption capacity of 373.14 mg/g for Pb^{2+} ions [21]. Zhang et al. functionalized reduced graphene oxide with 4-sulfophenylazo, achieving maximum adsorption capacities of 689 mg/g for Pb^{2+}, 59 mg/g for Cu^{2+}, 66 mg/g for Ni^{2+}, 267 mg/g for Cd^{2+}, and 191 mg/g for Cr^{3+} [22]. Additionally, Vilela et al. designed a graphene-based self-propelled microbot system capable of removing 80% of Pb^{2+} ions from water [23], while Yang et al. successfully used graphene oxide-sodium alginate beads to remove Mn^{2+} ions with an adsorption capacity of 56.49 mg/g [24]. Developing planar adsorbing materials based on fullerenes, optimized for adsorption, filtration, and

structural properties, also represents a promising direction in adsorption technologies [25-27]. More specifically, incorporating fullerenes into polymer matrices has been shown to enhance the sorption properties of these materials, enabling the effective extraction of heavy metal ions from aqueous electrolyte solutions [25]. In turn, Liang et al. studied the interactions between C60 fullerene and heavy metal ions (Cd, Cu, and Pb) to assess their effects on the uptake, transportation, and accumulation of these coexisting pollutants in four rice cultivars grown in agricultural soil throughout the entire rice life cycle [27]. They found, that the bioaccumulation of Cd^{2+} in the panicles of rice was significantly reduced when exposed to 1000 mg/kg C60 [27].

Despite the efficacy of carbon-based nanomaterials for the adsorption of heavy metals from water they also have several limitations such as i) tendency to aggregate in most solvents and form tangled network structures due to their hydrophobic nature, which can reduce their effective surface area and, consequently, their adsorption efficiency [15,19]; and ii) dependence of the rate of heavy metal adsorption of carbon-based nanomaterials from the medium pH and temperature [15,19]. Functionalizing carbon-based nanomaterials with polymers may help overcome these drawbacks, empowering their broad application. In this respect, the protein biopolymers have emerged as ideal candidates for conjugation with carbon nanomaterials due to their biological compatibility, structural and chemical variabilities. The special properties of protein and carbon nanomaterials can benefit each other giving rise to systems with a diverse chemical, electronic, catalytic, and biological properties. However, to the best of our knowledge, little is known about the intermolecular interaction of heavy metal ions in the presence of protein-carbon nanomaterials.

The present study is aimed to investigate the molecular interactions between the heavy metals and nanostructures based on the carbon nanomaterials (fullerenes C24, C60 and single-walled carbon nanotube) and β-lactoglobulin using the molecular docking technique.

MOLECULAR DOCKING STUDIES

The fullerene and nanotube structures were generated using the Nanotube Modeler software (version 1.8.0). More specifically, the carbon nanomaterial structures were defined by entering specific parameters into the Nanotube Modeler, including the number of carbon atoms, type of nanomaterial, chirality, and symmetry. The fullerenes with 24 and 60 carbon atoms (C24 and C60, respectively) and a single-walled carbon nanotube with a chirality of 10 and tube length 25 Å were composed. To ensure accuracy and reliability, the generated structures were validated using standard techniques, such as energy minimization.

The heavy metal salt structures (AsO_4, $Cd(NO_3)_2$, $Fe(NO_3)_3$, $NiSO_4$, $PbSO_4$, $PtCl_4$) were built in MarvinSketch (version 18.10.0) and optimized in Avogadro (version 1.1.0) [28,29]. The three-dimensional X-ray crystal structure of bovine β-lactoglobulin was obtained from the Protein Data Bank (https://www.rcsb.org/) using the PDB ID 1QG5. The docking of the carbon nanomaterial+protein+heavy metal complexes was carried out using the web-based HDOCK server. The docking studies were performed in two steps. Initially, the "blind docking" modeling was used to determine the most energetically favorable complexes of fullerenes and carbon nanotube with the protein. Next, the lowest binding energy conformer was selected for each docking simulation and was applied for further docking analysis with the heavy metal salts. The protein-ligand interaction profiler PLIP (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index) was used to further characterize the carbon nanomaterial+protein+heavy metal complexes [30].

RESULTS AND DISCUSSION

Due to their exceptional optical, electrical, chemical, mechanical, and thermal properties, carbon-based nanomaterials have gained significant attention in recent decades and have been utilized across various fields, including electronic devices, healthcare, energy, and environmental protection, among others. However, the high surface area of carbon-based units leads to strong attractive forces between them, causing aggregation and poor solubility, which can hinder their application [15,19]. Covalent functionalization with various polar groups and moieties [15,19] or hybridization with polymers can help mitigate these issues [15, 24,25]. In this context, protein biopolymers have emerged as ideal candidates for conjugation with carbon-based nanomaterials to enhance their dispersibility and material properties [31,32]. Before fabricating such nanomaterials for specific purposes, it is reasonable to assess the potential interaction modes between carbon-based structures, proteins, and targeted ligands using computational tools, particularly molecular docking techniques. This study aims to evaluate the feasibility of creating carbon-based nanomaterials (fullerenes C24 and C60, and single-walled carbon nanotubes) functionalized with β-lactoglobulin for heavy metal detection using molecular docking techniques. The choice of β-lactoglobulin for functionalizing carbon-based materials is based on its recently demonstrated effectiveness in developing nanocomposites for the detection and adsorption of heavy metal ions [33]. More specifically, a hybrid activated carbon membrane containing β-lactoglobulin amyloid fibrils appeared highly effective for the removal of heavy metal ions from wastewater [33].

Initially, to explore the molecular-level interactions between β-lactoglobulin and carbon-based nanomaterials materials, molecular docking calculations were conducted using the HDOCK server, with the main emphasis on determining the positioning of the CNs on the protein surface along with the specific amino acid residues and the types of interactions that contribute to the formation of the most energetically stable complexes. The obtained docking results indicate that the binding of C24 fullerene is stabilized by the hydrophobic interactions with the residues GLN_{35A}, TYR_{42A}, TRP_{61A}, THR_{154A} (Figure 1). The C60-protein complexation was presumably driven by the hydrophobic interactions with

the residues PHE$_{151A}$, ASN$_{152A}$, and THR$_{154A}$ of the helical β-lactoglobulin region. In addition, the C60 complexation was additionally stabilized by the π-stacking with the PHE$_{151A}$. As seen from Figure1 (panel c), the carbon nanotube formed stable contacts with the outer surface of the protein presumably through the hydrophobic interactions with TRP$_{61A}$, LEU$_{149A}$, PHE$_{151A}$, ASN$_{152A}$, THR$_{154A}$, π-stacking with PHE$_{151A}$ and the π-Cation Interactions with ARG$_{40A}$. The obtained results align well with numerous studies that categorize the binding interactions between carbon-based nanomaterials and proteins into three main subgroups: hydrophobic interactions (nonpolar solvation), π–π stacking (between sp^2 carbon structures and aromatic residues of proteins), and van der Waals forces (occurring between the surfaces of the interacting molecules) [34-37]. More specifically, the predominant role of the hydrophobic interactions in the complexation of carbon nanotubes with β-lactoglobulin [37] and blood proteins [38] was reported previously. In addition, Karchemsky et al. demonstrated the adsorption of carbon nanotubes on the β-lactoglobulin surface is a diameter-selective [37]. The docking scores of the obtained complexes were decreased in the following raw β-lactoglobulin+F24 (-113.16) → β-lactoglobulin+F60 (-121.71) → β-lactoglobulin+nanotube (-262.14). The observed decrease in docking scores with the increasing size of the carbon-based nanomaterials can be attributed to their larger surface area, which provides more binding sites for interactions.
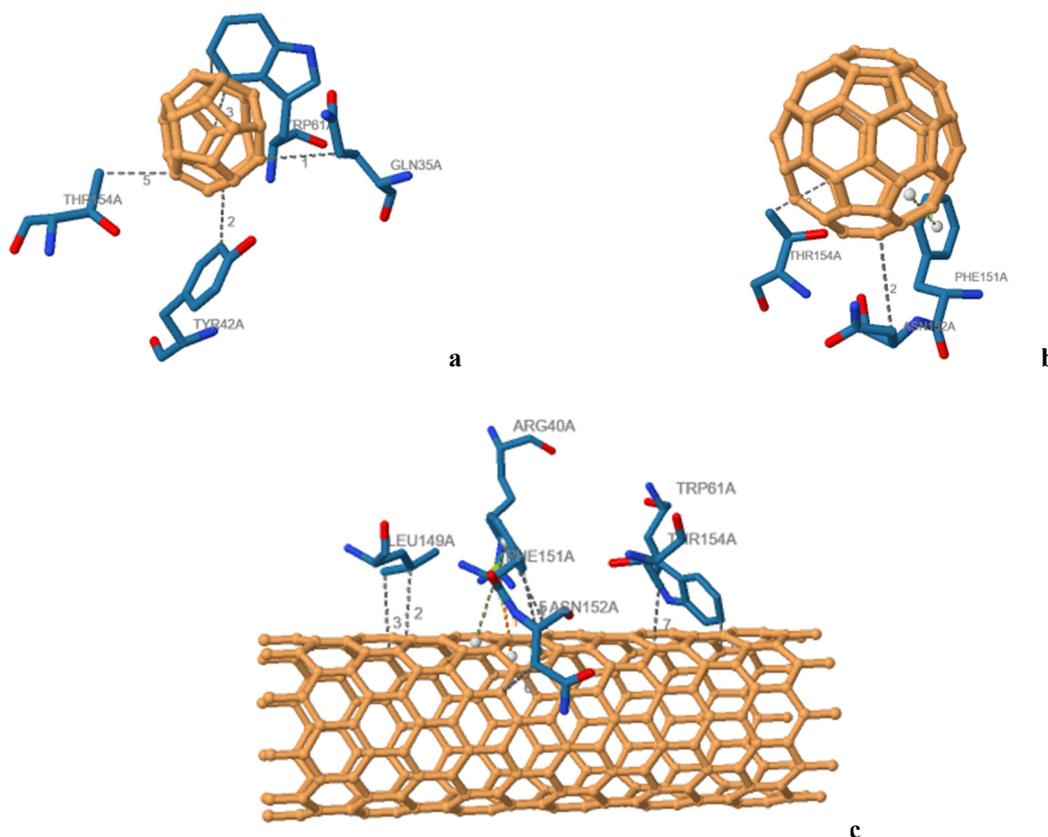
Figure 1. The binding interactions for the complexes between the β-lactoglobulin, fullerenes C24 (a), C60 (b) and carbon nanotube (c)

At the next step, the lowest binding energy conformers from the nanostructure-protein docking were selected and further used for the docking with the set of heavy metal salts. Presented in Figure 2 are the results of the analysis of the most energetically favorable complexes obtained after the docking in HDOCK and their characterization in the protein-ligand interaction profiler PLIP (Table 1). It was observed that in the F24- and F60-containing nanosystems, the protein binding sites for the investigated metal salts are located in close proximity to each other and the fullerenes. More specifically, our docking results indicate that in the F24-lactoglobulin system AsO$_4$, Cd(NO$_3$)$_2$, Fe(NO$_3$)$_3$, PbSO$_4$ tend to form contacts with both the fullerene and the protein amino acid residues. Meanwhile, the heavy metal salts NiSO$_4$, and PtCl$_4$ penetrate deeper into the protein interior, interacting exclusively with β-lactoglobulin. In turn, for the C60-containing systems all salts form the intermolecular contacts with both the protein and the carbon nanomaterials. The PLIP analysis indicates that the interactions of heavy metal salts in F24 and F60 systems are stabilized presumably by the hydrogen bonds with the SER$_{21A}$, GLN$_{59A}$, THR$_{154A}$ and ALA$_{67A}$ residues. An exception was PtCl$_4$, where complexation appeared to be driven primarily by hydrophobic interactions. In addition, the PLIP results indicate that PbSO$_4$ and NiSO$_4$ form a salt bridge with ARG$_{40A}$. The analysis of the docking results for the carbon nanotube-protein systems revealed that: 1) Cd(NO$_3$)$_2$ and Fe(NO$_3$)$_3$ interact with the nanotube and the β-lactoglobulin with the salt-protein complexation driven presumably by the hydrogen bonds with the residues ARG$_{40A}$, TYR$_{42A}$, GLN$_{59A}$, TRP$_{61A}$, THR$_{154A}$; 2) PtCl$_4$ binds

to the β-lactoglobulin through the hydrophobic interactions with THR_{154A}; 3) the AsO_4, $NiSO_4$, $PbSO_4$ do not interact with the protein and possess preferential binding to the nanotube interior. Overall, as shown in Table 1, the docking score for all carbon-based materials is changed in the same salt raw: $PtCl_4 \rightarrow PbSO_4 \rightarrow NiSO_4 \rightarrow AsO_4 \rightarrow Cd(NO_3)_2 \rightarrow Fe(NO_3)_3$.

F24

F60

nanotube
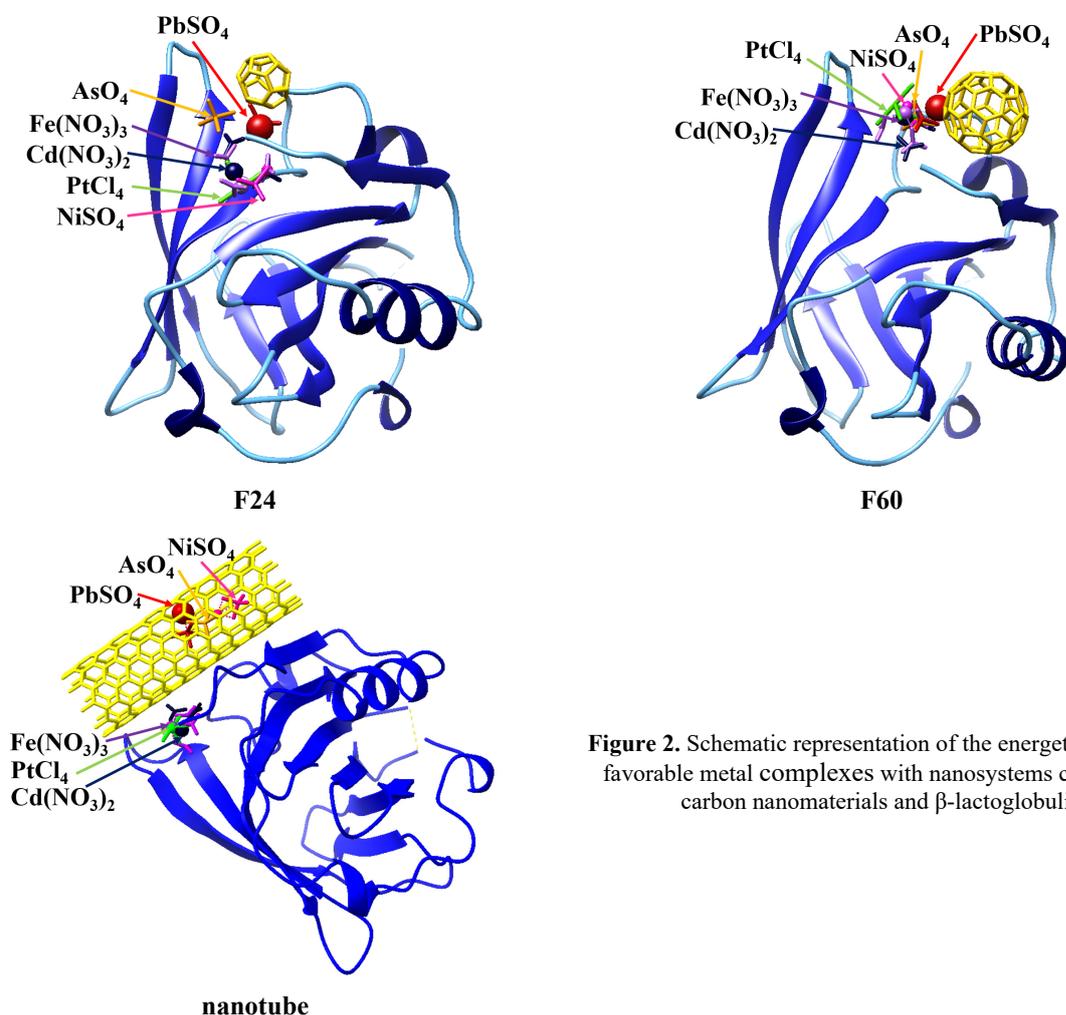
Figure 2. Schematic representation of the energetically most favorable metal complexes with nanosystems containing carbon nanomaterials and β-lactoglobulin

According to the previous studies, the complexation of heavy metal ions with carbon-based materials can be described by at least 5 different mechanisms: 1) physical adsorption assuming the diffusion and deposition of heavy metal ions into pores of an adsorbent without forming chemical bonds with the adsorption capacity dependent on the carbon nanomaterial pore size and surface area [39-41]; 2) ion exchange between the divalent metal cations with protons from the oxygen-containing functional groups of carbon nanomaterial (−COOH, −OH) [39, 42]; 3) surface complexation for the carbon nanomaterials carrying the functional group suitable for the forming multi-atom structures with metal ions [43,44]; 4) electrostatic interaction between the negatively charges groups of carbon nanomaterial and cations [39,40]; 5) precipitation (heavy metal ions can form solid precipitates or coprecipitate with other ions on the adsorbent surface) [39]. Given the unmodified unit (no oxygen-containing, charged groups) used for the creation of carbon-based nanomaterials in our study, the binding of the AsO_4, $NiSO_4$, and $PbSO_4$ to the interior of carbon nanotube can be described by the diffusion of heavy metals into the pores.

Notably, the adsorption mechanism of protein-based composites varies depending on the metal (its valence state, ionic radius, and charge-accepting ability) and the protein properties (amino-acid sequence, the accessibility of the potential metal-binding sites) [45-50]. For heavy metal ions, the main mechanisms include [49-50]:

    i)   Chemical complexation/chelation occurs due to the abundant –COOH and $–NH_2$ groups of the protein-based composites, which coordinate with metal ions to form N-metal and C– –O-metal complexes.

    ii)   the electrostatic interaction is attributed to the free ionizable –COOH and $–NH_2$ groups, which could generate positive or negative charges to attract heavy metals;

    iii)   the ion exchange of H^+ and OH^-, generated from –COOH and $–NH_2$ in the water environment.

Numerous studies indicate the predominant role of heavy metals' inherent chemistry in their interactions with proteins [45-51]. More specifically, the Hard Acid Soft Base theory determines the cations as acids, classifying all metals as hard, soft and borderline [51]. According to the Hard Acid Soft Base theory, hard acids prefer to bind to hard bases and soft acids prefer to bind to soft bases [51]. Proteins containing the amino acid residues possess a higher binding ability

to the "soft" metals (Pt^{2+} and Cd^{2+}) in comparison with "hard" metals (Fe^{3+}, As^{3+}) [51]. The preference mentioned above is linked to differences in their preferred binding mechanisms: metal chelation primarily maintains the structural integrity of protein-soft metal complexes, while electrostatic interactions play a key role in binding "hard" metals [51].

Table 1. Amino acid residues participating in the formation of the most energetically favorable metal-nanosystem complexes

Carbon nanomaterial	Heavy metal salt	Docking score	Amino acid residues forming contact with heavy metals
F24	AsO_4	-63.81	GLN_{59A}, ALA_{67A}
	$Cd(NO_3)_2$	-105.40	SER_{21A}, GLN_{59A}, THR_{154A}
	$Fe(NO_3)_3$	-135.62	SER_{21A}, GLN_{59A}, THR_{154A}
	$NiSO_4$	-62.08	SER_{21A}, THR_{154A}
	$PbSO_4$	-51.66	GLN_{35A}, SER_{36A}, ARG_{40A}, TRP_{61A}
	$PtCl_4$	-39.41	TYR_{20A}, TYR_{42A}, PHE_{151A}
F60	AsO_4	-70.00	GLN_{35A}, TYR_{42A}, TRP_{61A}, ARG_{40A}
	$Cd(NO_3)_2$	-108.99	TRP_{61A}, GLN_{35A}, ARG_{40A}, TYR_{42A}, THR_{154A}
	$Fe(NO_3)_3$	-148.40	GLN_{35A}, ARG_{40A}, TYR_{42A}, GLN_{59A}, THR_{154A}
	$NiSO_4$	-65.54	TYR_{42A}, ARG_{40A}
	$PbSO_4$	-57.80	GLN_{35A}, TYR_{42A}, ARG_{40A}
	$PtCl_4$	-42.29	GLN_{35A}, TYR_{42A}, TRP_{61A}, THR_{154A}
NT	AsO_4	-87.49	ND
	$Cd(NO_3)_2$	-130.37	TYR_{42A}, GLN_{35A}, TYR_{42A}, THR_{154A}
	$Fe(NO_3)_3$	-167.95	ARG_{40A}, TYR_{42A}, GLN_{59A}, TRP_{61A}, THR_{154A}
	$NiSO_4$	-94.50	ND
	$PbSO_4$	-73.49	ND
	$PtCl_4$	-54.67	THR_{154A}
ND means "not determined"			

Our docking results indicate that hydrogen bonding and hydrophobic interactions, play a predominant role in the complexation of heavy metal + β-lactoglobulin + carbon-based material systems. The docking simulations were conducted using heavy metal salts, which inherently contain both Lewis acids and Lewis bases. Notably, systems containing soft metals, such as $PtCl_4$ and $Cd(NO_3)_2$, demonstrated a stronger interaction with the protein than with the carbon-based nanomaterials. In contrast, $PbSO_4$, which includes the borderline Pb^{2+} ion and the hard SO_4^{2-} base, exhibited a higher binding affinity to the carbon-based materials across all studied systems. Interestingly, AsO_4 was found to interact more efficiently with carbon nanotubes than with fullerenes. In fullerene-containing systems, the binding primarily occurred with β-lactoglobulin. The above finding suggests that the size, shape, and surface properties of carbon-based materials significantly impact the nanocomposite's ability to interact with different heavy metals. This characteristic is highly advantageous for developing selective metal detection platforms. However, further detailed research is necessary to elucidate the precise role of carbon-based materials in the formation of protein-CN nanocomposites for the adsorption and detection of heavy metals.

CONCLUSIONS

To summarize, in the present study the docking technique was used to investigate the interactions of heavy metal salts (AsO_4, $Cd(NO_3)_2$, $Fe(NO_3)_3$, $NiSO_4$, $PbSO_4$, $PtCl_4$), carbone-based nanomaterials (fullerenes C24 and C60 and single-walled carbon nanotube) and β-lactoglobulin. It was found that: 1) the size, shape, and surface properties of carbon-based materials have a substantial impact on the ability of β-lactoglobulin-CNM complexes to interact with different heavy metals; 2) different heavy metal salts show distinct preferences for the various nanosystems; 3) hydrogen bonding and hydrophobic interactions are crucial in the complexation of heavy metal salts with β-lactoglobulin and carbon-based materials. Overall, these findings provide valuable insights into the design of protein-CNM systems for the detection and removal of heavy metals.

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ДОСЛІДЖЕННЯ МЕТОДОМ МОЛЕКУЛЯРНОГО ДОКІНГУ ФУНКЦІОНАЛІЗОВАНИХ БІЛКАМИ ВУГЛЕЦЕВИХ НАНОМАТЕРІАЛІВ ДЛЯ ДЕТЕКТУВАННЯ ТА ВИДАЛЕННЯ ВАЖКИХ МЕТАЛІВ

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Вуглецеві наноматеріали (ВН) зарекомендували себе надзвичайно ефективними для видалення важких металів із забрудненої води та навколишнього середовища завдяки своїм унікальним структурним і хімічним властивостям. Однак гідрофобна природа ВН і їхня схильність до агрегації в більшості розчинників створюють значні труднощі для їх практичного застосування. Функціоналізація вуглецевих наноматеріалів за допомогою білків є перспективним вирішенням цих проблем, що може призвести до створення систем з безпрецедентною ефективністю. Перед тим як створювати білково-ВН системи для виявлення та видалення важких металів, важливо оцінити афінність зв'язування металів та можливі взаємодії за допомогою комп'ютерних методів. У цьому дослідженні була використано метод молекулярного докінгу для вивчення взаємодій між солями важких металів (AsO₄, Cd(NO₃)₂, Fe(NO₃)₃, NiSO₄, PbSO₄, PtCl₄), вуглецевими наноматеріалами (фулерени C_{24} і C_{60}, а також одностінні вуглецеві нанотрубки) і β-лактоглобуліном. Результати докінгу показали, що:1) розмір, форма та поверхневі властивості вуглецевих матеріалів суттєво впливають на здатність комплексів β-лактоглобуліну з ВН взаємодіяти з різними важкими металами; 2) афінність солей важких металів до створених наносистем в значній мірі варіюється; 3) водневі зв'язки та гідрофобні взаємодії відіграють суттєву роль у комплексоутворенні солей важких металів з β-лактоглобуліном та вуглецевими матеріалами.

Ключові слова: *вуглецеві наноматеріали; важкі метали; β-лактоглобулін, молекулярний докінг*