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INTERACTION OF HEAVY METALS WITH β-LACTOGLOBULIN: MOLECULAR DYNAMICS STUDY

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β-Lactoglobulin (β-lg), the predominant whey protein, is renowned for its nutritional and functional attributes, including its ability to bind hydrophobic and charged molecules. These properties make β-lg a promising candidate for applications such as drug delivery systems, nutraceutical carriers, and nanocomposites for environmental remediation, particularly in detecting and removing heavy metals. Despite its potential, the impact of heavy metal binding on β-lg's structure and stability remains insufficiently explored, posing challenges for its advanced applications. In this study, molecular dynamics (MD) simulations were employed to investigate the structural and dynamic responses of β-lg to the binding of heavy metal ions—Cd^{2+}, Ni^{2+}, Co^{3+}, Pb^{2+}, and Pt^{2+}. A series of 200-ns MD simulations for the metal-protein complexes was conducted at 300 K using GROMACS software and the CHARMM General Force Field. Key structural parameters analyzed included backbone root-mean-square deviation (RMSD), radius of gyration (Rg), solvent-accessible surface area (SASA), and root-mean-square fluctuations (RMSF). The results demonstrated that binding of Cd^{2+}, Ni^{2+}, Co^{3+}, Pb^{2+}, and Pt^{2+} destabilized the protein's structure, with notable effects observed in critical regions such as the EF loop, H-strand, and AB loop. The extent of destabilization varied depending on the specific heavy metal ion. These findings emphasize the need for detailed residue-level analyses to fully elucidate the structural changes induced by metal binding and their implications for β-lg's functional properties. This work provides valuable insights into the behavior of β-lg under heavy metal binding and lays the groundwork for developing β-lg-based nanosystems for environmental and biomedical applications.
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Rapid industrialization and urbanization have significantly increased the discharge of heavy metals into global water resources. Even at trace concentrations, heavy metals pose serious health risks by damaging bones, nerves, and enzymes, and contributing to various severe health conditions [1,2]. To address this issue, a range of methods has been developed over the years for the removal of toxic heavy metals, including ion exchange [3,4], reverse osmosis [5], complexation precipitation [6,7], and adsorption [8,9]. Among these, adsorption stands out as an efficient, environmentally sustainable, and cost-effective solution, particularly when low-cost adsorbents are utilized [8,9]. Within the realm of adsorption, biosorption has gained prominence. This approach employs biopolymer-based biomass—such as chitosan, alginate, cellulose, starch—to bind and remove pollutants passively from aqueous solutions [10,11]. Among various biosorbents, protein-based nanomaterials have emerged as particularly promising candidates for heavy metal adsorption, owing to their diverse amino acid functional groups, which exhibit strong metal-binding properties [12-21]. The ability to induce the supramolecular assembly of protein molecules and tailor the structural properties of newly formed two- or three-dimensional structures at the molecular level opens new avenues for designing customized materials for various applications. A wide range of structures, including fibrils, spherical condensates, and gels, can be generated, spanning sizes from the nanoscale to the macroscopic scale. These supramolecular assemblies' structure, mechanical properties, charge, polarity, water accessibility, and stability can be precisely adjusted by controlling the growth conditions [12-21]. Recent advancements in protein-based adsorbents, including proteins and peptides functionalized derivatives and protein-derived nanomaterials have demonstrated exceptional removal efficiencies for a wide range of heavy metals [12-21]. To exemplify, Yu et al. developed a hybrid membrane for detecting and separating mercury ions by combining gold nanoclusters, bovine serum albumin (BSA) nanofibers, and graphene oxide with a mercury removal efficiency of up to 90.4% [13]. The soy protein-based polyethylenimine hydrogel was found can effectively adsorb Cu(II) ions from aqueous solution even in the presence of co-existing competitive heavy metal ions, such as Zn(II), Cd(II), and Pb(II) [14]. The excellent Pb (II) ions adsorption efficiency was previously observed for bovine serum albumin micro-sized amyloid-like spherical particles [15] and soy protein microsponges [16]. Costal et al demonstrated the efficiency of tunable biopolymers based on elastin-like polypeptides composed of either one or two hexahistidine clusters for Cd(II) removal [17]. In particular, hybrid membranes combining activated carbon and amyloid fibrils, self-assembled from various proteins such as β-lactoglobulin, soy protein, globulin, silk, and albumin, have shown exceptional effectiveness in purifying wastewater contaminated with heavy metals and radioactive compounds. [18-21]. More specifically, a hybrid membrane with activated carbon successfully removed over 99.5% of gold, mercury, lead, and palladium, both individually and in mixed aqueous solutions, and achieved 99% removal of arsenites and arsenates from prepared solutions and real contaminated water [18-21]. The isothermal thermal calorimetry (ITC) measurement performed by Peydayesh et al. also demonstrated

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the more than 99% removal efficiencies of hybrid protein-carbon membranes also for chromium, nickel, silver, and platinum ions [18].

Among the various proteins employed in the composition of protein-based nanomaterials for heavy metal removal, β-lactoglobulin has emerged as a particularly promising, readily available, and low-cost candidate [18–20]. Numerous studies have highlighted β-lactoglobulin's ability to interact with various heavy metal ions, especially in the context of amyloid-carbon hybrid membranes [18–20]. However, to the best of our knowledge, little is known about the intermolecular interactions between heavy metal ions and β-lactoglobulin. Motivated by the protein's capacity to bind specific heavy metal ions, in our recent studies we identified the binding sites for heavy metal ions (Cu^{2+}, Fe^{3+}, Mg^{2+}, Mn^{2+}, Zn^{2+}, Cd^{2+}, Fe^{2+}, Ni^{2+}, Hg^{2+}, Co^{2+}, Cu^{+}, Au^{+}, Ba^{2+}, Pb^{2+}, Pt^{2+}, Sm^{3+}, and Sr^{2+}) on β-lactoglobulin and explored the possible interactions involved in protein-ion binding [22]. Building on our previous work, the present study employs molecular dynamics simulations to elucidate the influence of selected heavy metal ions (Cd^{2+}, Ni^{2+}, Co^{3+}, Pb^{2+}, Pt^{2+}) on the structure and dynamics of β-lactoglobulin.

MOLECULAR DYNAMICS SIMULATIOS

Molecular dynamics simulations and trajectory analyses were conducted using GROMACS software (version 5.1) with the CHARMM36m force field. The three-dimensional X-ray crystal structure of bovine β-lactoglobulin was obtained from the Protein Data Bank (https://www.rcsb.org/) under c. Input files for the MD simulations were prepared using the Solution Builder module of the web-based CHARMM-GUI interface [23]. The system was solvated using a TIP3P water rectangular solvation box, ensuring a minimum distance of 10 Å between the protein and the box edges. Six distinct ion-protein systems were prepared for simulation. The control system consisted of the protein and 7 Na+ ions, added to neutralize the protein's net charge. Heavy metal ions were introduced into the system and randomly distributed according to the following scheme:

Table 1. The composition of systems containing bovine β-lactoglobulin and heavy metal ions

Metal	Number of metal ions	Number of Cl^-
Cd^{2+}:	4	1
Co^{3+}:	3	2
Ni^{2+}:	4	1
Pb^{2+}:	4	1
Pt^{2+}:	4	1

The molecular dynamics simulations and analysis of the trajectories were performed using the GROMACS software (version 2023.3) with the CHARMM36m force field in the NPT ensemble with the time step for MD simulations 2 fs. The calculations were performed at a temperature of 300 K. The minimization and equilibration of the systems were carried out during 50000 and 250000 steps, respectively. The Berendsen algorithm was used for thermostat and barostat during the equilibration phase. The LINCS algorithm was applied to constrain the lengths of hydrogen-containing bonds.The time interval for MD calculations was 200 ns. The GROMACS commands gmx rms, gmx gyrate, gmx rmsf were used to calculate the protein backbone root-mean-square deviation (RMSD), protein radius of gyration (R_g), root-mean-square fluctuations of the C-alpha atoms (RMSF). Visualization of the snapshots of the MD runs and analysis of the protein secondary structures and protein solvent-accessible surface area (SASA) were performed in VMD.

RESULTS AND DISCUSSION

β-lactoglobulin

β-Lactoglobulin, the predominant protein in whey, is highly valued in the food industry for its remarkable nutritional and functional properties. Each β-lactoglobulin monomer consists of 162 amino acids, has a molecular weight of 18.3 kDa, and features a hydrophobic core formed by eight anti-parallel β-strands, creating a characteristic calyx-shaped β-barrel [24]. These structural attributes, combined with its multiple high-affinity binding sites for hydrophobic and charged molecules, make β-lactoglobulin an excellent candidate for advanced applications. Notably, it shows great potential in the development of: i) nanocarriers for delivering drugs, nutraceuticals, and bioactive compounds; and ii) nanocomposites for detecting and removing heavy metal ions [18-20, 25]. The development of lactoglobulin-based nanosystems for environmental applications relies on a detailed understanding of the protein's metal-binding properties. Experimental approaches to identifying protein metal-binding sites, characterizing protein-metal interactions, and studying metal-induced changes in protein structure can be challenging. However, computational methods offer a relatively fast and efficient alternative for characterizing protein-ligand interactions.

In this study, molecular dynamics simulations were conducted to examine the influence of selected heavy metal ions (Cd^{2+}, Ni^{2+}, Co^{3+}, Pb^{2+}, and Pt^{2+}) on the structure and dynamics of β-lactoglobulin. Representative snapshots from a 200 ns simulation of heavy metal binding to β-lactoglobulin are presented in Figure 1. Notably, the binding propensity of these metals to the protein under identical simulation conditions differed significantly. Cd^{2+} and Co^{3+} exhibited a higher binding affinity for β-lactoglobulin compared to c ions added to the system formed stable interactions with the protein within the first 30 ns of the simulation and remained within the protein's binding pocket for the remainder of the

simulation time. In contrast, only two Ni^{2+} ions and one Pb^{2+} or Pt^{2+} ion established metal-protein contacts throughout the simulation. These findings align with previous experimental observations by Peydayesh et al., who demonstrated a stronger binding affinity of silver compared to chromium for similar protein systems [18]. Moreover, the higher binding propensity of Cd^{2+} relative to Pb^{2+} has also been reported for β-lactoglobulin dimers and β-lactoglobulin-carbon composite nanomaterials [26].

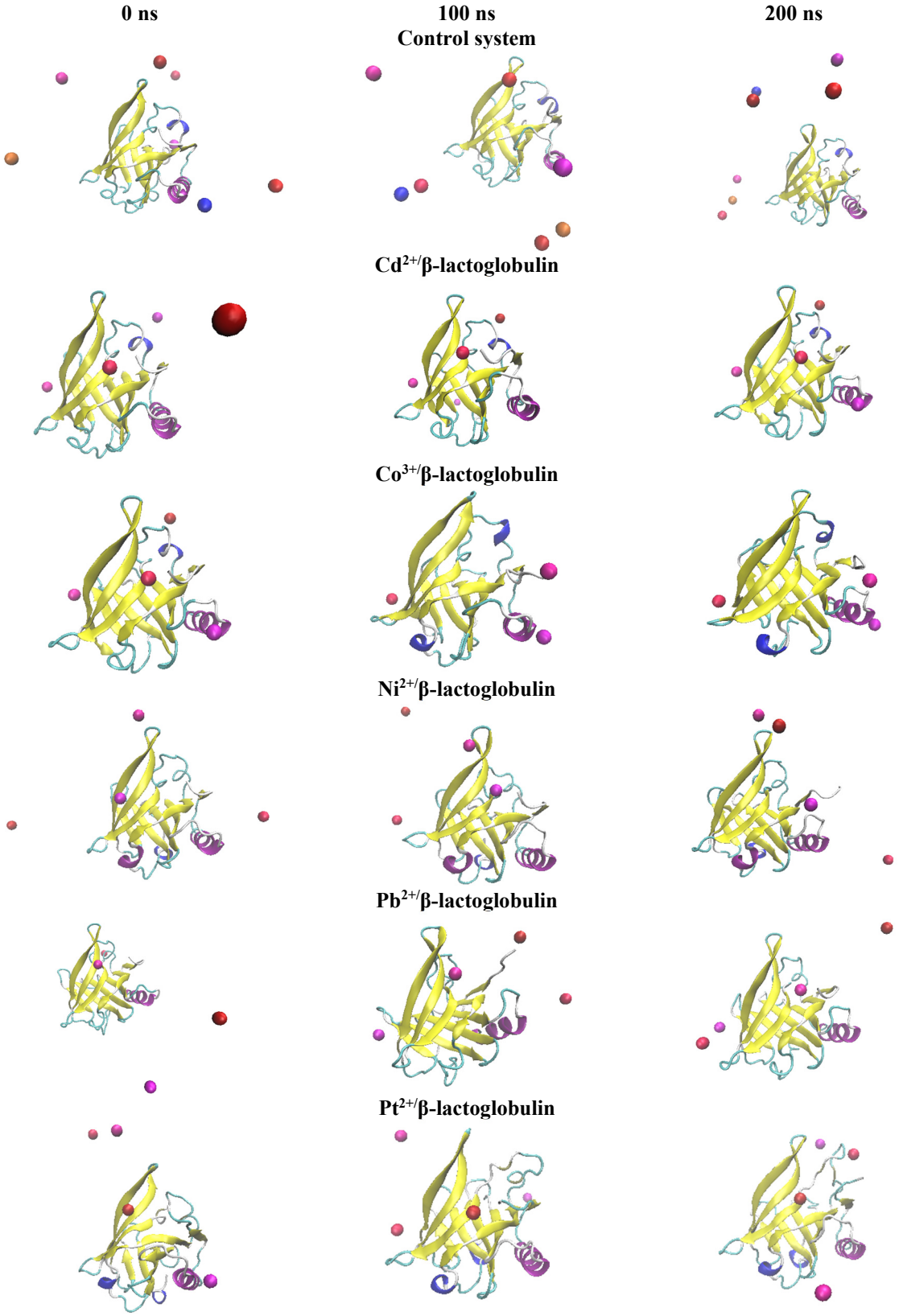

Figure 1. Representative snapshots of the metal-protein complexes

The selectivity and strength of interactions between metal ions and protein binding sites can be effectively explained using the Hard and Soft Acids and Bases (HSAB) theory [27]. According to HSAB theory, metal ions preferentially bind to protein sites that match their relative hardness or softness. In general, the interactions between hard acid metals and hard basic sites are predominantly ionic, whereas covalent bonds typically form between soft acid metals and soft basic sites. These distinct interaction types influence the structural integrity of proteins. For example, metal complexes interacting with bovine serum albumin (BSA) can disrupt disulfide bonds, leading to changes in the protein's secondary structure, including a significant loss of α-helical content and eventual unfolding [29]. Furthermore, metal-protein interactions can alter the local polarity around exposed tryptophan residues due to molecular rearrangements, affecting the protein's structural and functional properties [29].

Therefore, in the initial stage of our study, we evaluated the overall stability of the protein over the simulation period by analyzing the time evolution of several structural parameters, including the protein backbone root-mean-square deviation (RMSD), radius of gyration (Rg), root-mean-square fluctuations (RMSF) of the C-alpha atoms, and solvent-accessible surface area (SASA). Figure 2 illustrates the temporal changes in the backbone RMSD, providing insight into the dynamic stability of the protein throughout the simulation.

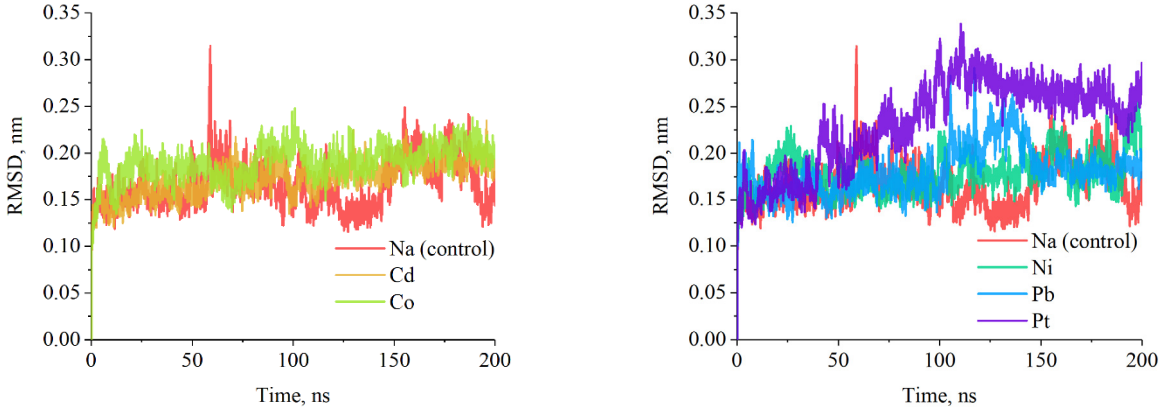

Figure 2. Time course evolution of the root-mean-square deviation

As shown in Figure 2, the calculated RMSD values for the Cd^{2+}, Ni^{2+}, and Co^{3+}-containing systems remained below 0.2 nm, except for brief fluctuations observed in the Ni^{2+}/lactoglobulin system during the first 50 ns and in the Co^{3+}/lactoglobulin system between 80 ns and 115 ns. In contrast, the Pb^{2+} and Pt^{2+} ion-protein systems exhibited less stable trajectories compared to the other heavy metals studied. The RMSD time profile for the Pb^{2+}/lactoglobulin system reveals two distinct phases: i) slight fluctuations around 0.18 nm during the first 100 ns of the simulation and ii) a transient increase in RMSD values to 0.22–0.25 nm over the subsequent 30 ns, followed by a decrease back to approximately 0.17 nm, where it stabilized and fluctuated for the remainder of the simulation. For the Pt^{2+}/lactoglobulin system, a significant increase in RMSD values was observed starting at ~30 ns. The RMSD then converged and equilibrated, fluctuating around an average value of 0.26 nm for the remainder of the simulation. The higher RMSD values observed in the Pt^{2+}/lactoglobulin and Pb^{2+}/lactoglobulin systems relative to their initial structures suggest potential conformational changes in the protein, with these changes being more pronounced in the presence of Pt^{2+}. However, the minimal fluctuations (small standard deviation) in backbone RMSD during the final 50 ns of the simulation indicate that the systems ultimately reached equilibrium and remained stable under the simulation conditions.

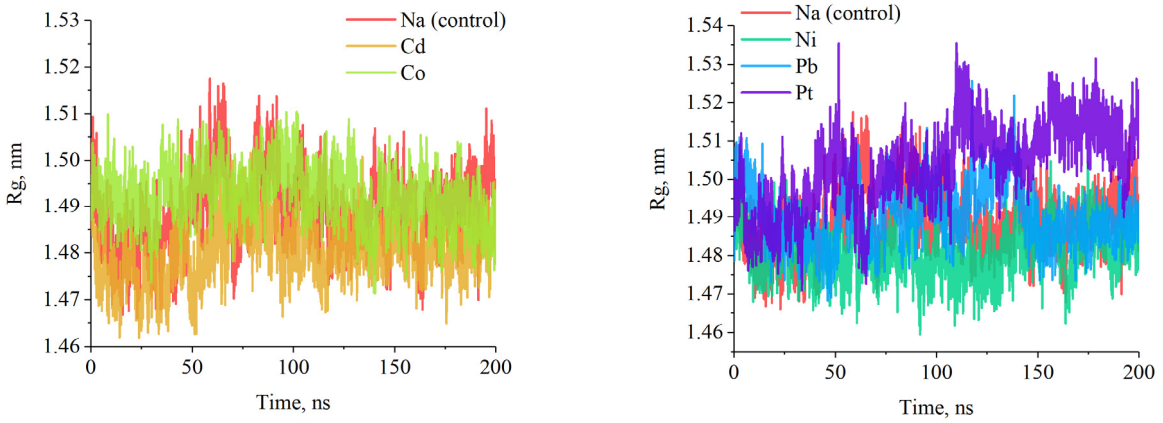

Figure 3. Time course evolution of the radius of gyration

The radius of gyration (Rg) is a key parameter for assessing a protein's structural compactness. Lower Rg values indicate a more tightly folded polypeptide chain, whereas higher Rg values reflect a more expanded or open protein

structure. The Rg for heavy metal/protein complexes was calculated and plotted over simulation time to evaluate changes in protein compactness, as illustrated in Figure 3. The results suggest that the protein structure remained relatively stable throughout the simulations, with an average Rg of 1.49 nm observed for all systems except for Pt^{2+}/lactoglobulin, which exhibited a slightly higher average Rg of 1.52 nm. However, specific trends in Rg patterns are noteworthy. The Rg values for Cd^{2+}, Ni^{2+}, Co^{3+}, and Pb^{2+} containing systems displayed a decreasing trend during the first 50 ns, indicating an initial increase in the structural compactness of lactoglobulin. Following this period, the Rg values stabilized, reflecting the preservation of compactness for the remainder of the simulation. A slight increase in Rg value was observed throughout the simulation for Pt^{2+}, suggesting the occurrence of potential Pt-induced spatial rearrangements in the side chains of amino acid residues and potentially within the secondary structures of β-lactalbumin.

The secondary structure of β-lactoglobulin (β-lg) consists of approximately 15% α-helix, 50% β-sheet, and 15–20% reverse turns [24]. Its globular structure is formed by nine β-strands (A–I) arranged into two β-sheets, along with three turns of α-helix. At neutral pH, these β-sheets form a conical barrel known as the calyx, with strand A linking the sheets on one side and strands D and E providing a secondary connection [24]. The α-helix is situated between strands A and H, followed by strand I. The protein's structure is stabilized by disulfide bonds: Cys106–Cys119 linking strands G and H, and Cys66–Cys160 linking strand D to the C-terminal [24].

To determine the dynamic behavior of amino acid residues, the RMSF values of the C-alpha atoms of protein in the presence of heavy metal ions were calculated (Figure 4).

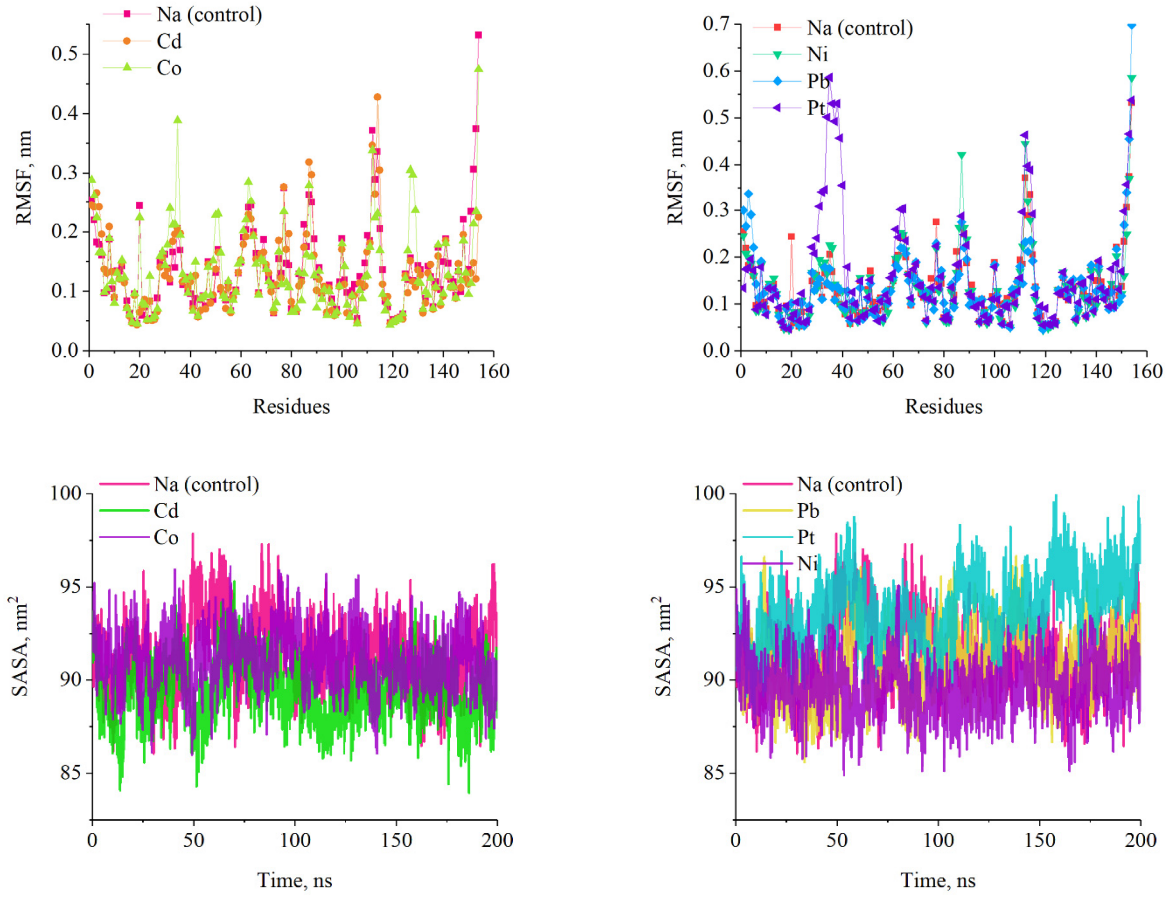

Figure 4. Time course evolution of the root-mean-square fluctuations and the solvent-accessible surface area for the metal-protein complexes

The RMSF analysis provided insights into the fluctuations of amino acid residues in all heavy-metal/protein systems under study, identifying regions of the protein that exhibited greater spatial fluctuations due to ion binding. Specifically, in the Pb^{2+}/lactoglobulin system, significant residue fluctuations were observed exclusively in the N-terminal region (residues V2–L10). Similar patterns of higher fluctuations in regions with minimal secondary structure were noted for other metal ions: Cd^{2+} (residues A86–E89), Co^{3+} (residues N63–C66 and P126–D130), Pt^{2+} (residues E62–D64 and E112–Q115), and Ni^{2+} (residues E112–Q115). Of particular interest is the EF loop (residues D85–E90), which acts as a gate regulating access to the binding site [24]. At low pH, this loop adopts a "closed" conformation, inhibiting or preventing ligand binding. Conversely, at high pH, the loop transitions to an "open" state, enabling ligands to penetrate the hydrophobic binding site [24]. The binding of all studied heavy metals, except Pb^{2+}, was associated with noticeable fluctuations in the H1 helical region (residues 30–36), with Pt^{2+} inducing the most significant changes. Interestingly, the

AB loop region plays a critical role in stabilizing the β-lactoglobulin structure through an ion pair interaction between Asp33 of one subunit and Arg40 of the other [24]. Thus, the observed increase in residue fluctuations within this region suggests that heavy metal ions may destabilize the tertiary protein structure by disrupting these key stabilizing interactions. Additionally, increased fluctuations in the amino acid residues of the H-strand region were observed in the presence of Cd^{2+}, Ni^{2+}, and Pt^{2+}. This region includes the Cys119 residue, which forms a disulfide bond with Cys106—a critical interaction that stabilizes the overall protein structure [24]. In addition, Co^{3+} binding to the β-lactoglobulin caused an increase in fluctuations in the amino acid residues of the B strand (residue E45-P50).

A key factor influencing the interfacial properties of proteins is their solvent-exposed surface. To evaluate changes in the environment of β-lactoglobulin residues during the simulation, the solvent-accessible surface area (SASA) per residue was calculated (Figure 4). The analysis revealed no significant differences in SASA values across most protein-metal complexes. For the majority of systems studied, SASA fluctuated within the range of 87–95. However, a slight increase in SASA was observed for the Pt^{2+}/lactoglobulin complex during the simulation, suggesting a potential alteration in protein conformation specific to the presence of Pt^{2+}.

Molecular dynamics simulations of β-lactoglobulin in the presence of heavy metals (Cd^{2+}, Ni^{2+}, Co^{3+}, Pb^{2+}, and Pt^{2+}) reveal their partial destabilizing effects on the protein's tertiary structure, even at low concentrations. The integrity of the tertiary structure is highly sensitive to the dihedral angles of amino acid side chains, which can be significantly altered upon metal binding [30,31]. These alterations disrupt torsional angles, disturb hydrogen bonding networks, and may propagate changes to secondary structural elements such as α-helices or β-sheets, ultimately affecting the protein's overall stability and conformation. Additionally, heavy metal binding has been shown to induce structural rearrangements by promoting the separation of non-polar groups from water, thereby encouraging the formation of new hydrophobic interactions [31,32]. While our results indicate that the secondary structure remains largely intact, the tertiary structure undergoes modifications due to metal interactions. However, further investigations are necessary to fully elucidate these structural changes and their implications for β-lactoglobulin functionality.

CONCLUSIONS

The present study utilized molecular dynamics (MD) simulations to explore the effects of heavy metal ion binding (Cd^{2+}, Ni^{2+}, Co^{3+}, Pb^{2+}, and Pt^{2+}) on the structure and dynamics of β-lactoglobulin. The 200 ns MD simulation results performed at 300 K using GROMACS software and the CHARMM General Force Field indicate that Cd^{2+} and Co^{3+} exhibited the strongest binding affinity among the studied metals, forming stable interactions within the protein's binding pockets. In contrast, Ni^{2+}, Pb^{2+}, and Pt^{2+} showed lower binding stability, with fewer ions maintaining contact throughout the trajectory. The analysis of root-mean-square deviation (RMSD) and radius of gyration (Rg) revealed varying degrees of structural destabilization upon metal binding. Pt^{2+} had the most pronounced destabilizing effect, as evidenced by increased RMSD and Rg values. Residue-level root-mean-square fluctuations (RMSF) analyses revealed that metal binding particularly affected regions important for β-lactoglobulin's stability including the EF loop, AB loop, H-strand, and H1 helix. Overall, the study underscores the sensitivity of β-lactoglobulin's tertiary structure to heavy metal binding. The destabilizing effects observed, particularly with Pt^{2+}, highlight the need for further residue-level investigations to fully elucidate the mechanisms underlying metal-induced structural changes.

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ВЗАЄМОДІЯ ВАЖКИХ МЕТАЛІВ З β-ЛАКТОГЛОБУЛІНОМ: ДОСЛІДЖЕННЯ МЕТОДОМ МОЛЕКУЛЯРНОЇ ДИНАМІКИ

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β-Лактоглобулін (β-lg), основний білок сироватки молока, відомий своїми винятковими харчовими та функціональними властивостями, зокрема здатністю зв'язувати гідрофобні та заряджені молекули. Завдяки цим властивостям β-lg є вкрай перспективним для розробки систем доставки лікарських препаратів і нанокомпозитів для екологічної ремедіації, зокрема для виявлення та видалення важких металів. Попри його потенціал, вплив зв'язування важких металів на структуру та стабільність β-lg залишається недостатньо вивченим, що створює труднощі для його практичних застосувань. У цьому дослідженні були використано метод молекулярної динаміки (MD) для аналізу структурних та динамічних реакцій β-lg на зв'язування важких металів—Cd^{2+}, Ni^{2+}, Co^{3+}, Pb^{2+} та Pt^{2+}. Серія 200-нс симуляцій MD для комплексів метал-білок проводилася при 300 K за допомогою програмного забезпечення GROMACS та силового поля CHARMM. Основними проаналізованими структурними параметрами були середньоквадратичне відхилення остову ланцюга, радіус інерції, площа поверхні, доступна для розчинника та середньоквадратичні флуктуації. Результати показали, що зв'язування Cd^{2+}, Ni^{2+}, Co^{3+}, Pb^{2+} та Pt^{2+} спричиняло дестабілізацію структури білка, із помітним впливом на EF-петлю, H-ланцюг та AB-петля білку. Ступінь дестабілізації залежав від конкретного іона важкого металу. Ці висновки підкреслюють необхідність детального аналізу на рівні залишків амінокислот для повного розуміння структурних змін, викликаних зв'язуванням металів, та їх впливу на функціональні властивості β-lg. Отримані результати мають важливе значення у контексті розуміння механізмів взаємодії β-lg з важкими металами і для розробки наносистем на основі β-lg для екологічних та біомедичних застосувань.

Ключові слова: *взаємодія білок-метал; важкі метали; молекулярна динаміка*