East European Journal of Physics. **2.** 470-475 (2024)
DOI:10.26565/2312-4334-2024-2-62 ISSN 2312-4334

DECIPHERING THE MOLECULAR DETAILS OF INTERACTIONS BETWEEN HEAVY METALS AND PROTEINS: MOLECULAR DOCKING STUDY

O. Zhytniakivska*, U. Tarabara, K. Vus, V. Trusova, G. Gorbenko
Department of Medical Physics and Biomedical Nanotechnologies, V.N. Karazin Kharkiv National University
4 Svobody Sq., Kharkiv, 61022, Ukraine
**Corresponding Author: olga.zhytniakivska@karazin.ua*
Received April 2, 2024; revised May 6, 2024; February, accepted May 26, 2024

Understanding the interaction of heavy metals with proteins is pivotal for unraveling their roles in biochemical processes and metal-induced diseases, with wide-ranging implications spanning medicine, environmental science, and biotechnology, thereby driving progress in therapeutics, pollution mitigation, and biomaterial innovation. In the present study the molecular docking technique was employed to identify and characterize the binding sites of the set of heavy metals (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+}) and proteins ((β-lactoglobulin, 7S globulin and glycinin from soybeans) to evaluate the impact of protein structure on their ion-binding abilities and selectivity. Our docking results indicate that essential and toxic heavy metals interact with multiple binding sites of proteins, presumably by electrostatic interactions and metal chelation with cysteine, aspartic acid, glutamic acid, and histidine amino acid residues. The comparison of binding residues favorable for heavy metal complexation among different proteins indicates that metals exhibit distinct preferences for various amino acid residues highlighting the importance of both the metal and the protein properties for stabilizing protein-metal complexation.
Keywords: *Protein-metal interaction; Heavy metals; Molecular docking*
PACS: 87.14.Cc, 87.16.Dg

Heavy metals, a loosely defined group of elements, including transition metals and some metalloids, typically have an atomic number greater than 20 and atomic density above 5 $g \cdot cm^{-3}$ [1,2]. While the classification of heavy metals as toxic, beneficial, or essential for living organisms is a topic of ongoing debate, certain heavy metals such as Mg^{2+}, Ca^{2+}, Fe^{3+}, Mn^{2+}, Co^{2+}, Cu^{2+} and Zn^{2+} are currently recognized as essential in a trace amount [2,3]. In contrast, non-essential heavy metal ions like Pb^{2+} and Hg^{2+}, are toxic even at trace levels, causing alterations to biochemical processes and potentially leading to various diseases in living organisms [4,5]. Aquatic organisms and humans are exposed to the influence of essential and non-essential heavy metals through multiple sources, including water, air, soil, and food [5]. Despite the numerous studies, the molecular mechanisms underlying heavy metal toxicity are not fully understood [6,7]. The primary factors by which heavy metals can possess their toxic effect are i) generation of reactive oxygen species and oxidative stress [8,9]; ii) disruption of membrane function and nutrient assimilation [10,11]; iii) DNA damage and impairment of DNA repair mechanism [12,13] and iv) protein function and activity perturbation [14,15]. It is well-established that proteins are primary targets of heavy metals. Metals can interfere with the biological activity of properly folded proteins through various interactions, including binding to free thiols or other functional groups, displacing essential metal ions in metalloproteins, or catalyzing the oxidation of amino acid side chains, to name only a few [14-16]. Understanding the interactions between proteins and heavy metals is not only crucial for comprehending their biochemical roles, regulation, and the molecular basis of metal-induced diseases, but also significantly important for medicine, environmental science, and biotechnology. More specifically, the integration of metal ions with protein systems led to the design of highly ordered protein-based hybrid nanomaterials possessing unique electric, optical, and electronic properties, high photostability, and biocompatibility, making them attractive for different applications in biological imaging, solar energy conversation, chemical sensing, to name only a few [17-23]. In particular, amyloid fibrils self-assembled from different proteins (β-lactoglobulin, globulin, silk, albumin, etc) have demonstrated remarkable efficacy in purifying wastewater contaminated with heavy metals and radioactive compounds [20-23]. Additionally, metal-binding proteins can be engineered to enhance the bioavailability of essential metals in nutritional supplements or for designing metal-based drugs with optimized efficacy and safety [24, 25]. Moreover, understanding the molecular mechanisms underlying the interactions between plant proteins and heavy metals is essential for developing effective phytoremediation strategies [26, 27]. The above application necessitates a comprehensive understanding of the protein's metal-binding capabilities. Experimental techniques, such as X-ray crystallography [28], NMR spectroscopy [29], electron microscopy [19], and absorption spectroscopy [30] have been found to offer the most reliable information for studying protein-metal interactions. Despite their precision and accuracy in identifying metal ions, these techniques have significant disadvantages, including high costs, lengthy execution times, and challenges. During the last decades computation methods have become invaluable tools for relatively quick and easy identification of metal-protein binding sites.

In the present study, we employed the molecular docking technique to evaluate the impact of protein structure on their ion-binding abilities and selectivity. More specifically, by varying both the protein amino acid composition (β-lactoglobulin, 7S globulin and glycinin from soybeans) and heavy metal ions (Cu^{2+}, Fe^{3+}, Mg^{2+}, Mn^{2+}, Zn^{2+}, Cd^{2+}, Fe^{2+},

Cite as: O. Zhytniakivska, U. Tarabara, K. Vus, V. Trusova, G. Gorbenko, East Eur. J. Phys. 2, 470 (2024), https://doi.org/10.26565/2312-4334-2024-2-62
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Ni^{2+}, Hg^{2+}, Co^{2+}, Cu^{+}, Au^{+}, Ba^{2+}, Pb^{2+}, Pt^{2+}, Sm^{3+}, and Sr^{2+}), we attempted to identify and characterize protein-ion binding sites.

MOLECULAR DOCKING STUDIES

The three-dimensional X-ray crystal structures of proteins were obtained from the Protein Data Bank (https://www.rcsb.org/) using the PDB IDs 3AUP, 1OD5 and 1QG5 for 7S globulin from soybean, glycinin, and bovine β-lactoglobulin, respectively. The chain A of the three-dimensional X-ray crystal structures of 7S globulin and glycinin, were selected for the docking studies. To define the most energetically favorable binding sites for the heavy metal ions on the proteins, molecular docking studies were performed using the MIB2 Metal Ion-Binding site prediction and modeling server [31]. The MIB2 employs the fragment transformation technique and the AlphaFold protein structure database for the precise binding site predictions for 18 metal ions, including Ca^{2+}, $Cu^{2+,}$ 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+} [31].

RESULTS AND DISCUSSION

β-lactoglobulin

β-lactoglobulin, a small globular whey protein with a molecular weight of approximately 18.4 kDa, is currently widely employed in the development of nanocomposites for the detection of heavy metal ions [22, 32]. More specifically, Zang and colleagues found, that β-lactoglobulin-stabilized fluorescent gold nanoclusters are promising for the selective nanomolar detection of Hg^{2+} in beverages, urine, and serum [32]. Peydayesh et al demonstrated the β-lactoglobulin amyloid fibril effectiveness in the removal of heavy metals by fabricating a hybrid activated carbon membrane [22]. Heavy metal ions have been found to adsorb efficiently and strongly onto β-lactoglobulin amyloid fibrils through robust supramolecular metal-ligand interactions with the magnitude of absorption dependent on the specific heavy metal [22]. Designing lactoglobulin-based nanosystems for heavy metal detection and targeted delivery requires a thorough understanding of the protein's metal-binding capabilities. These insights are essential for optimizing the design and effectiveness of such nanosystems in various applications. In the present study, we employed a molecular docking technique to identify β-lactoglobulin-metal binding sites. Docked positions of heavy metal ions in the β-lactoglobulin structure corresponding to the best docking score are presented in Figure 1.

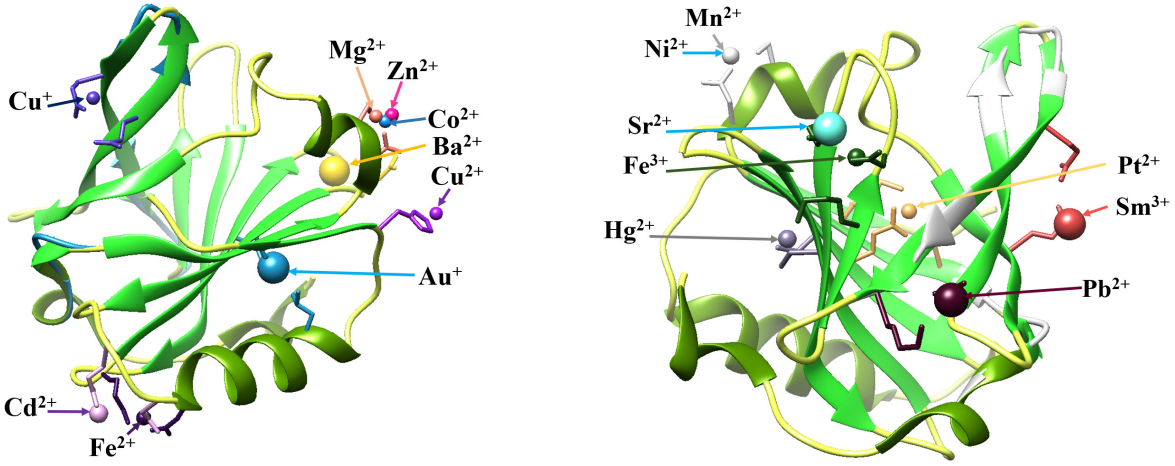

Figure 1. Docked positions of heavy metal ions in the 3D β-lactoglobulin structure corresponding to the best docking score

The protein β-lactoglobulin comprises 162 amino acid residues, featuring one free cysteine and two disulfide bonds [33]. Three-dimensional crystallographic studies have revealed that β-lactoglobulin predominantly adopts a β-sheet configuration, comprising nine antiparallel β-strands (A to I), where strands A-D form one surface of the β-barrel (calyx), while strands E-I constitute the opposite surface [33]. The sole α-helical segment, consisting of three turns, is located at the COOH terminus and lies on the outer surface of the calyx, following strand H [33]. Our docking results indicate that essential and toxic heavy metals bind to multiple binding sites of β -lactoglobulin, presumably into the outskirts of the β-barrel. The amino acid residues, participating in the interaction of metal ions with protein are presented in Table 1. More specifically, the essential heavy metals such as Mn^{2+}, Co^{2+}, $Mg^{+,}$ and Zn^{2+} interact with the strand A of the β-barrel with the residue Asp and Ser. Notably, the amino acid residues such as Ser or Asp contain nitrogen or oxygen atoms that play an electron donor role in the ligand-protein interactions. In addition, our docking results indicate that Zn^{2+} is energetically favorable to interact with the F strand of protein. The presence of two sets of independent binding sites for zinc was experimentally observed for the other whey protein α-lactalbumin [34]. The highly toxic metal ions such as Pb^{2+}, Pt^{2+}, and Sm^{3+} form contacts with the B-strand of protein, whereas Cd^{2+} and Hg^{2+} preferably interact with the residues near the H-strand. The negatively charged glutamic acid participates in the Pb^{2+}, Pt^{2+}, Sm^{3+} and Cd^{2+} ion-protein complexation. In turn, our docking results indicate that highly toxic Hg^{2+} interacts with the polar cysteine and hydrophobic valine and leucine.

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

Metal	β-lactoglobulin	glycinin	7 S globulin
Cu^{2+}	Pro144, His146	Gln36, His173, Glu175, His21, Asn34, His37	His23, Pro269, Cys81, His90
Fe^{3+}	Lys83, Glu89, Asp96, Asp98	His211, Gln215, Glu221	Gln69, Glu113, Cys65, Asn92
Mg^{2+}	Asp28, Ile29	Asp231, Asp232, Asp121, Glu333, Asn334	Asp114, Val115, Asp17, Ser19, Thr20
Mn^{2+}	Asp28, Ser30	Asp413, Gly414	Asp374, Arg377, His215, Asp216
Zn^{2+}	Asp28, Ser30, Asp96, Asp98	His173, Glu175, Asp20, His37	His215, Asp216, Cys65, Ser67
Cd^{2+}	Glu127, Asp129, Glu131, Lys135	Asp413, Gly414, Asp231, Glu233	Gln171, His175, Asn50, Ser140, Cys141
Fe^{2+}	Lys10, Glu127, Asp129	Lys210, His211, Gln215	His66, His76, Cys78
Ni^{2+}	Asp28, Ser30	Arg115, His116, Lys210, His211	His388, Asp396, His76, Cys78, Cys94
Hg^{2+}	Cys106, Leu117, VAl118, Cys119	Phe82, Cys85, Cys327	Phe64, Cys65, Cys78
Co^{2+}	Asp28, Ser30, Glu127, Asp129	Asp20, His37, Lys210, His211	Cys81, His90, Ser389, His390
Cu^{+}	Gln59, Cys66	Cys9, Cys42, Pro425	Cys70, His76, Cys94, Cys81, His90
Au^{+}	Cys106, Lys140	Cys85, Glu323, Pro19, Gln36, His37	Cys141, Ala142, Ser187, Glu368, Cys394
Ba^{2+}	Glu108, Asn109, Gln115	Thr136, Gly137, Asp138, Glu139	Asp334, Lys335, Glu333
Pb^{2+}	Glu51, Glu52, Asp53, Glu74	Asp232, Arg234	Cys65, Cys78, Gly302, Lys303, Cys304, Cys345
Pt^{2+}	Glu51, Glu52, Met24, Arg40, Lys95	Asp232, Lys235	Gln275, Met353, His270, Met349
Sm^{3+}	Glu44, Glu45, Gln68	Asp231, Glu233, Asp232, Lys235	Asp374, Arg377, Glu52, Gln53
Sr^{2+}	Asp85, Leu87 Glu89	Asp20, His21, Thr32, Glu172, Asp157, Gln158, Thr176	Asp41, Ser265, Ser267

According to numerous studies, heavy metals bind to proteins through different intermolecular interactions, presumably electrostatic interactions, and metal chelation [21-32]. Several factors influence the binding of metals to proteins, including i) the properties of the metal such as its valence state, ionic radius, and charge-accepting ability and ii) the protein properties, such as amino-acid sequence, the accessibility of the potential metal-binding groups, type of the interactions stabilizing protein-metal complexation, etc [21-32]. According to the Hard Acid Soft Base theory describing the interaction of heavy metals based on their inherent chemistry, the proteins possess a higher binding ability to the "soft" metals (Cd^{2+}, Hg^{2+}, Cu^{+}, Au^{+}, Pt^{2+}) in comparison with "hard" metals (Ca^{2+}, Mg^{2+}, Mn^{2+}, and Sr^{2+}) [35]. The above preference is connected with the differences in their binding mechanism: metal chelation is predominant in maintaining the structural integrity of the protein-soft metal complexes, whereas electrostatic interactions are responsible for the "hard" metal binding [35]. As can be seen from Table 1, glutamic acid participates in the Pb^{2+}, Pt^{2+}, Sm^{3+} and Cd^{2+} ion-protein complexation, whereas the "hard metals" were found to form contacts presumably with the negatively charged aspartic acid, which is in good agreement with the Hard Acid Soft Base theory [35]. Notably, our docking results demonstrated the involvement of the Lys, Leu and Val amino acid residues in the metal-protein interaction of "soft" (Cd^{2+}, Hg^{2+}, Cu^{+}, Au^{+}, Pt^{2+}) and borderline (Ni^{2+}, $Cu2^{+}$, Pb^{2+}) Lewis acids indicating the possible role of the hydrogen bonds, hydrophobic and van der Waals interactions on the stabilization of protein-metal complexes.

7S globulin from soybean

The 7S globulin is one of the major globulins found in soybean seeds [36]. Despite its dual subunit composition and oligomeric assembly, the protein possesses a compact structure, comprising β-sheets and a few α-helices, with its most notable feature being 12 cysteine residues [36]. These cysteines, conserved among homologous proteins, form a network of five intra-chain and one inter-chain disulfide bridges [36]. Recently it was demonstrated, that soy c exhibits excellent metal-chelating properties [37]. Moreover, Li et al/ showed the ability of soy protein-based polyethyleneimine hydrogel to selectively adsorb and recycle copper in wastewater [38]. Additionally, the soy protein hollow microspheres were highly effective for the sorption of metal ions, with the absorption capacity dependent on the heavy metal [21]. Despite numerous studies demonstrating the potential of soy protein-based nanocomposites for purifying water from heavy metals, the factors responsible for their metal selectivity require further investigation. In an attempt to understand the mechanism of the complexation of different heavy metal ions with the 7S globulin, we identified their preferred binding sites (Figure 2).

Our docking results indicate that essential and toxic heavy metals bind to multiple binding sites of soy protein globulin 7S and have at least two high-score binding sites. More specifically, as seen from Figure 2 and Table 1, all heavy metals (excepting Ni^{2+}, Au^{+}, Pb^{2+}, Pt^{2+}, and Sm^{3+}) form contacts presumably with the amino-acid residues of α-subunit (residues 25-275). The toxic metals Ni^{2+}, Au^{+}, Pb^{2+}, Pt^{2+}, and Sm^{3+} were found to interact with both α-subunit (residues 25-275) and low-molecular-weight β-subunit (residues 276-427), with the binding preferences higher for the latter. As seen in Figure 2, the heavy metal formed stable contacts with the residues belonging presumably to the β-strands of the protein. However, we found that Cd^{2+} and Fe^{2+} were energetically favorable to interact with the α-helixes. In addition,

Ba^{2+} and Ni^{2+} are positioned in the $3_{10\text{-helix}}$ of protein. Importantly, cysteine residues are among the amino-acid residues participating in stabilizing protein-metal complexes for all metals except Mg^{2+}, Ba^{2+}, and Pt^{2+}. The cysteine residues forming the disulfide bonds within the protein are responsible for the stability of the soy protein globulin 7S [36].

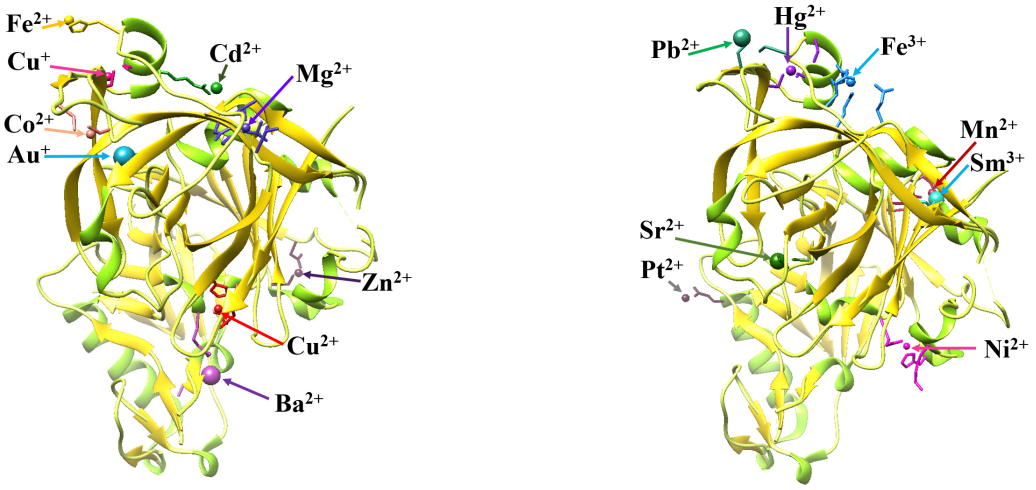

Figure 2. Schematic representation of the energetically most favorable metal complexes with globulin (chain A) obtained using the Metal Ion-Binding site prediction and modeling server.

Glycinin from soybean

Soybean glycinin, a member of the 11S globulin family, is a hexameric protein with a molecular weight of approximately 360 kDa, composed of five subunits: A1aB1b, A1bB2, A2B1a, A3B4, and A5A4B3 [39]. It is formed by the stacking of two trimers, each consisting of three subunits [39]. These subunits are composed of an acidic polypeptide (A) with a molecular weight of 35 kDa and a basic polypeptide (B) with a molecular weight of 20 kDa, which are linked by disulfide bonds [39]. The soybean glycinin protomer consists of four visible and four disordered regions (residues 1–6, 93–107, 179– 199, and 252–320) comprising 27 strands and 7 helices which are folded into two jelly-roll-barrel domains and two helix domains [39]. As seen from Figure 3, the heavy metals, formed stable contacts with the various residues present in the ordered glycinin regions and don't interact with the disordered regions. The main results obtained from molecular docking studies are:

i) Heavy metals excluding Fe^{3+}, Mn^{2+}, Zn^{2+}, Fe^{2+}, Ni^{2+}, Co^{2}+, Ba^{2+}, Pb^{2+}, Pt^{2+}, and Sm^{3+} exhibit at least two energetically favorable binding sites;
ii) Mg^{2+}, Cd^{2}, Pb^{2+}, and Pt^{2+} tend to interact with the residues Asp 232, Glu 233, Arg 234 and Lys 235 located near the second helix of protomer;
iii) Fe^{3+}, Fe^{2+}, Ni^{2+}, and Co^{2+} show preferential binding sites comprising the amino acid residues 211-215 (Lys, His, Gln) within the helix region. Ni^{2+} additionally forms the high-score complex with the residues in the proximity to β-strand F (Arg15 and His 116), while Co^{2+} interacts also with the residue of β-strand A.
iv) Mn^{2+}, Cd^{2+} bind to the strand region containing residues Asp 413 and Gly 414.

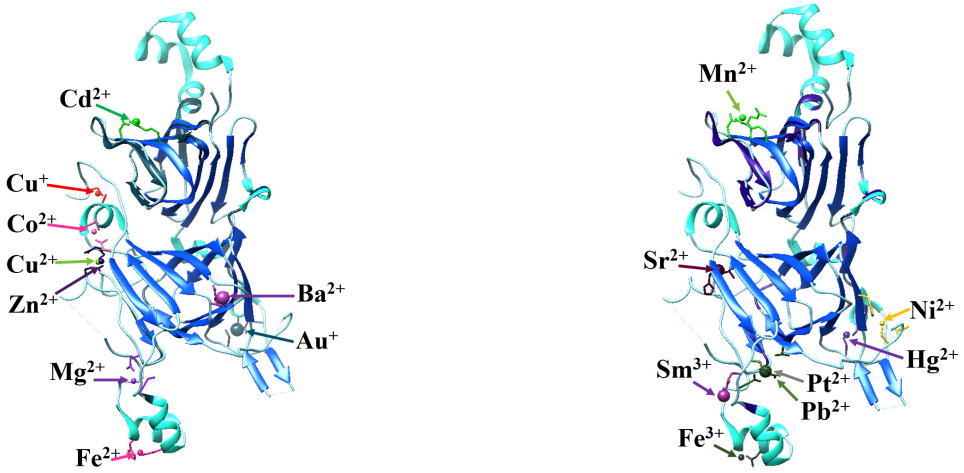

Figure 3. Schematic representation of the energetically most favorable metal complexes with glycinin (chain A) obtained using the Metal Ion-Biding site prediction and modeling server.

The comparison of the binding residues favorable for the complexation of heavy metals between the proteins indicates that metals yield various binding preferences for different amino-acid residues. More specifically, for Fe^{3+} was

energetically favorable to form contacts with Lys, Glu and Asp amino acids of β-lactoglobulin, whereas His, Gln and Gln, Cys were responsible for metal-protein complexation of glycinin and 7S globulin, respectively. Zn^{2+} interacts with the Asp and Ser residue of β-lactoglobulin, His, Glu of glycinin, whereas for the 7S globulin, cysteine residues were also involved in the complexation. Although electrostatic interactions and metal chelation are the preferential binding modes of metals, our docking results indicate the importance of the hydrogen bonds, hydrophobic and van der Waals interactions on the stabilization of protein-metal complexes.

CONCLUSIONS

In the present study, the molecular docking technique was employed to evaluate the impact of protein structure on their ion-binding abilities and selectivity. By varying both the protein amino acid composition (β-lactoglobulin, 7S globulin and glycinin from soybeans) and 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+}), the protein-ion binding sites were identified.The docking results suggest that both essential and toxic heavy metals interact with multiple protein binding sites, primarily through electrostatic interactions and metal chelation involving cysteine, aspartic acid, glutamic acid, and histidine residues. The comparison of binding residues favorable for heavy metal complexation among different proteins indicates that metals exhibit distinct preferences for various amino acid residues highlighting the importance of both the metal properties (valence state, charge-accepting ability, etc) and the protein properties, (amino-acid sequence, the accessibility of the potential metal-binding groups, etc).

Acknowledgements

This work was supported by the Ministry of Education and Science of Ukraine (the project "Development of novel means of medical diagnostics by biomedical nanotechnologies and modern ultrasonic and fluorescence methods" and the project "Development of economically affordable nanosystems for rapid identification and purification of water from heavy metal ions based on carbon nanoallotropes and amyloids from organic waste".

ORCID

Olga Zhytniakivska, https://orcid.org/0000-0002-2068-5823; **Uliana Tarabara,** https://orcid.org/0000-0002-7677-0779
Kateryna Vus, https://orcid.org/0000-0003-4738-4016; **Valeriya Trusova,** https://orcid.org/0000-0002-7087-071X
Galyna Gorbenko, https://orcid.org/0000-0002-0954-5053

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ДОСЛІДЖЕННЯ МОЛЕКУЛЯРНИХ ДЕТАЛЕЙ ВЗАЄМОДІЇ МІЖ ВАЖКИМИ МЕТАЛАМИ ТА БІЛКАМИ: МОЛЕКУЛЯРНИЙ ДОКІНГ

О. Житняківська, У. Тарабара, К. Вус, В. Трусова, Г. Горбенко

Кафедра медичної фізики та біомедичних нанотехнологій, Харківський національний університет імені В.Н. Каразіна м. Свободи 4, Харків, 61022, Україна

Розуміння взаємодії важких металів з білками є ключовим для розкриття їх ролі у різноманітних біохімічних процесах в медицині, екології та біотехнологіях, що сприяє розробці принципово нових терапевтичних стратегій та інноваційних гібридних біоматеріалів. У даній роботі з використанням методу молекулярного докінгу було визначено та охарактеризовано центри зв'язування важких металів (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+}) з білками (β-лактоглобулін, 7S глобулін і гліцинін з соєвих бобів) для оцінки впливу структури білка на їхню метал-зв'язувальну здатність та селективність. Отримані результати молекулярного докінгу вказують на взаємодію життєво важливих та токсичних важких металів з різними зв'язувальними сайтами білків, ймовірно, через електростатичні взаємодії та хелацію металів з амінокислотними залишками цистеїну, аспарагінової кислоти, глутамінової кислоти та гістидину. Порівняння залишків з якими взаємодії метал між різними білками, свідчить про роль різних амінокислотних залишків, підкреслюючи важливість як властивостей металу, так і білка для стабілізації білок-металевого комплексоутворення.

Ключові слова: *взаємодія білок-метал; важкі метали; молекулярний докінг*