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# Understanding of Protein Adhesion to PLGA Through Molecular Docking Analysis

**Didem Mimiroglu[1,a], Sema Zabcı[2,b,*]**

[1] *Department of Biochemistry, Faculty of Science, Sivas Cumhuriyet University, 58140, Sivas,Türkiye*

[2] *Department of Molecular Biology and Genetics, Faculty of Science and Letters, Baskent University, 06790 Ankara, Türkiye*

**Corresponding author*

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**ABSTRACT**

In tissue engineering, cellular adhesion is a multistep process which occurs between the cell and the specific molecules and proteins that are adsorbed from biological fluids to the material surface. Therefore, it is essential to understand the protein adsorption level and which protein can bind efficiently to the surface of the fabricated material. Although many studies in literature showing quantification of protein adsorption levels by chemical methods and some instrumental techniques, there is a notable gap in the literature regarding the application of molecular docking analysis to identify which proteins can bind effectively to material surfaces, together with the specific interactions and orientations involved. Towards this goal, the present study aimed to evaluate the interactions between FDA approved biomaterial poly(lactic-co-glycolic acid) (PLGA) surface and specific proteins which are commonly found in cell culture medium for in vitro studies, and integrins which are associated with cellular adhesion. The results showed that PLGA exhibited strong binding affinity to both BSA and integrin β2, while less stable bindings were performed by hemoglobin and α2-macroglobulin proteins. These results indicate that how molecular recognition via docking process is important for fabricating biomaterials in tissue engineering applications.

***Keywords:*** Molecular docking, PLGA, Cellular adhesion, Serum proteins

[a] dmimiroglu@cumhuriyet.edu.tr https://orcid.org/0000-0003-2838-9719 [b] semazabci@baskent.edu.tr https://orcid.org/0000-0002-8886-0077

## Introduction

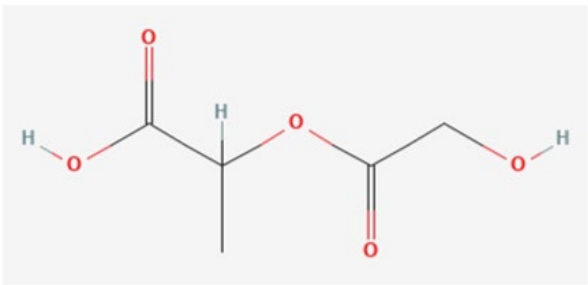
In recent years, tissue engineering is one of the fast-growing area in the regenerative medicine which is related with developing materials for repairing damaged tissues, organs and cellular transplantations in the body[1,2]. Therefore, there are many necessary features which are being biodegradable, biocompatible, enhancing cellular migration and adhesion, being biomimetic, upregulating cellular proliferation etc. to be considered depending on the cells, tissues and organs to be gained in the fabrication of biomaterials for tissue engineering [2–4]. Among these features, enhancing cellular adhesion, which is specific interactions between cells and biomaterials, is essential for improving cellular migration, proliferation [2].

Cellular adhesion is a process which can occur between cell-cell and cell-extracellular matrix (ECM) via the specific interactions between cellular receptors and appropriate molecules on the other surface to that the cells will adhere. Integrins which are heterodimer transmembrane proteins consisting of α and β subunits, are the main cellular adhesion molecules involving in the adhesion process [4–6]. In tissue engineering side, the adhesion occurs between the cellular surface and the fabricated material. In cellular adhesion, the cells do not interact with the bare material surface and while adhesion process is performed to the fabricated material, initially, water and protein adsorption from biological fluids take place on the surface of the material [7]. Therefore, in biomaterials used in tissue engineering, the adsorption level of the proteins from the culture medium and integrin binding which could be influence due to material surface chemistry, hydrophilicity, topography, stiffness and etc., should be primarily evaluated *in vitro.* Among these properties, fabricating nano and micron-sized topographic structures to the material surfaces, cell adhesion can be increased owing to the hydrophilic feature of the surface, increased surface area, and higher concentrations of protein adsorption. For instance, Yang et al. (2021) studied differences of the adsorption profiles of myoglobin (MBG), thyroglobulin (TGL) and bovine serum albumin (BSA) on the smooth and nanotopographical $SiO_x/Si$ and $TiO_x/Ti$ surfaces. Among these proteins, it was found that $TiO_x/Ti$ nanotopographical surface had higher thickness value for MBG protein compared to smooth surface, and it was statistically significant [8]. In the different study, Zhao et al. (2022) investigated BSA and human serum fibronectin (HFN) adsorption profiles on the flat and different nanostructured $TiO_2$ surfaces. It was observed that all nanostructured surfaces were superhydrophilic with PBS incubation. Additionally, the highest BSA and HFN adsorption profiles were found for three different nanostructured $TiO_2$ surfaces compared the flat surface [9]. In another study, Dabare et al. (2021) fabricated different nanotopographical via producing and immobilization gold nanoparticles (AuNPs) on the surfaces and they evaluated albumin adsorption levels on these surfaces. It was observed that the amount of albumin were 4-fold higher for the highest nanotopographical surface compared to lowest surface which results were found in-line with increasing surface area levels [10]. All of these results were based on the quantifying absorption levels of proteins by using chemical methods such as ellipsometry, Bradford and BCA protein assays. In addition, molecular docking is another procedure which is exploring and evaluating the protein interactions with specific substrates such as proteins, peptides ligands, molecules and etc. This computational technique is related with predicting binding affinity and also most suitable fitted orientation between these molecules [11–13]. Thus, molecular docking can be very important for tissue engineering in terms of evaluating how proteins effectively bind to the materials surface and which non-covalent interactions can be responsible for binding [14]. As a result of this, it can be examined which proteins might be essential for cellular adhesion process. In the one of our study, nanophase topographies were fabricated on poly (lactic-co-glycolic acid) (PLGA) for neural tissue engineering applications. It was observed that there was an increase for the surface area and protein adsorption levels for the nanophase topographical PLGA surfaces than the smooth sample. Additionally, nanophase topographical surfaces expressed lower contact angle which means that the surfaces had hydrophilic characteristics and functional groups such as -C-H, -C=O, -$CH_3$, and -$CH_2$ as identified by FTIR analysis [15]. Therefore, the aim of the study is to investigate the interactions between PLGA polymer surface which is approved by the US Food and Drug Administration (FDA) and specific proteins mainly found in *in vitro* cell culture medium, specifically BSA, hemoglobin, and $\alpha$2-macroglobulin, as well as integrin proteins which is related with cellular adhesion process. Since the initial step in cellular adhesion involves the adsorption of serum proteins onto the material surface [7], understanding how these proteins interact with PLGA is important. To gain insights into these molecular interactions in detail, molecular docking method were performed. Binding scores and weak interactions such as hydrogen bonds, van der Waals forces and hydrophobic bonds were analyzed and compared to show the nature and extent of protein-surface interactions. This study provides a molecular level insight into protein-ligand interactions, enabling the prediction of cell-surface interactions. Owing to the molecular docking analysis, the significant residues in binding could be identified, which might assist the design of more effective biocompatible materials in the future.

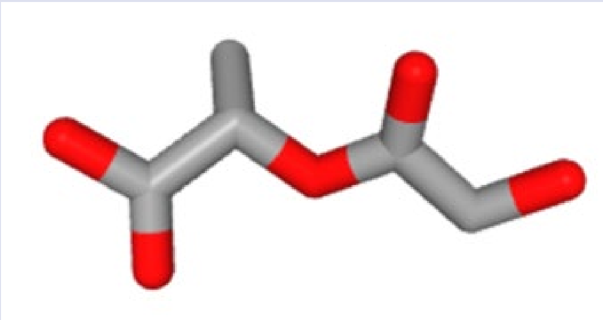
## Methods

The Molecular Docking method was carried out using the AutoDock Vina algorithm of the SWISS-DOCK webserver (https://www.swissdock.ch/) due to its strong performance in pose prediction and scoring accuracy across diverse protein-ligand complexes [16,17]. AutoDock Vina's performance has been benchmarked against large datasets and showed strong accuracy in sampling and scoring [18]. Furthermore, SwissDock 2024 is a userfriendly web tool offering both fast and high precision docking algorithms, supporting non-covalent and covalent ligand docking to various biological targets, including proteins, nucleic acids, and cofactors [19].

The three-dimensional crystal structures of Bovine Serum Albumin (PDB ID: 4F5S), Bovine Hemoglobin (PDB ID: 2QSS), Bovine $\alpha$2-macroglobulin (PDB ID: 1AYO) and integrin $\beta$2, talin 1 (PDB ID: 8FSE) were obtained from Protein Data Bank (https://www.rcsb.org/) with their respective identification numbers. These structures were prepared for docking by eliminating heteroatoms, water molecules, and bound ligands. Also, missing H atoms were added by using the BIOVIA Discovery Studio Visualizer (Ver 4.5). The SMILES format of the ligand, PLGA, was obtained from PubChem (CID: 23111554) (https://pubchem.ncbi.nlm.nih.gov), and its copolymer form, poly(D,L-lactic acid-co-glycolic acid), was used in this study. This copolymer shares similar functional groups (–OH and –COOH) with the monomeric form, which are primarily responsible for hydrogen bonding and electrostatic interactions with the target proteins (Figure 1) [19]. The size of the docking grid box was set to 20×20×20 Å, while the center coordinates of the grid were adjusted for each protein's active site (Table 1).



(a)



(b)

Figure 1. 2D and 3D structures of PLGA. The chemical structure of the PLGA copolymer is shown in both (a) 2D and (b) 3D representations.

All output results from the docking analysis were visualized and analyzed using the BIOVIA Discovery Studio Visualizer (Ver 4.5). Multiple binding poses were evaluated for each protein–ligand interaction, and the best binding pose, depending on the lowest binding score (kcal/mol), was selected for further analysis. The number of weak interactions was also evaluated to provide a deeper understanding of the interactions. The surface of the ligand, PLGA, was displayed by H-bond in the active pockets to show interactions more clearly. Furthermore, 2-D and 3-D interaction images were generated using the same visualizer tool.

Table 1. Box Center Coordinates of the Proteins

| Proteins | Box Center Coordinates (XYZ) |
|---|---|
| Bovine Serum Albumin | 8, 19, 123 |
| Bovine Hemoglobin | -1.60, 6.70, 24.40 |
| Bovine $\alpha$2-macroglobulin | 6.74, 72.30, 3.70 |
| Integrin $\beta$2, Talin 1 | -3.03, -44.50, -20.93 |

## Results and Discussion

It is very important for cellular adhesion to the material surface to occur efficiently in terms of biocompatibility, cellular migration and proliferation while fabricating biomaterials for tissue engineering applications. Therefore, there are many studies which are related with how cellular adhesion to the material surface occurs, which proteins play important roles and the concentration of adsorbed proteins are associated with cellular adhesion. However, there is a limited numbers of research studies on which bonds bind the proteins adsorbed to the surface before cellular adhesion, and thus which one interacts more effectively with the material surface. For this reason, PLGA which is FDA approved and widely used in tissue engineering, especially for neural cells, was preferred in the study, and it was studied to investigate how proteins, specifically important for cellular adhesion, bind to the surface by molecular docking. In our previous study, it was observed that PLGA film surfaces with nanophase topographies had more hydrophilic surface properties and higher surface area compared to control group [15]. Accordingly, the results were evaluated by comparing the surface binding properties of proteins with molecular docking.

In silico studies, many researchers have used the monomeric structures of the polymers in docking studies due to the challenges of the polymeric structures including large size and conformational complexity. In recent study, Ünlü et al. (2023) modeled the interaction between polyvinyl alcohol (PVA) and a Group IA bacteriocin by docking the PVA monomer to the protein, demonstrating that monomer-based docking can give meaningful results about polymer–protein interactions [20]. Similarly, Saadati et al. (2021) investigated protein interactions with polyvinylidene fluoride (PVDF) membranes by using monomer-based ligand models, which allowed them to understand atomic-level interaction with human serum proteins [21]. Consistently, Patnode et al. (2021) utilized a computational protein–ligand docking approach to model the interactions of natural modifiers (glycerol, sorbitol, and cellulose) with plant-derived proteins such as soy and zein in order to design of bioplastic films [22]. These studies collectively support the methodological approach used in the present work, where the monomeric unit of PLGA was selected for molecular docking.

The molecular docking results of PLGA model with the active site of the BSA had a maximum binding energy of -5.11 kcal/mol (Table 2). It was observed that BSA had the highest binding capacity for the ligand, PLGA compared the other cell culture medium proteins. For BSA, several significant hydrogen bonds were identified. Conventional hydrogen bonds were observed between the side chain residues Asn390, Arg409, and Ser488 of BSA and the oxygen atoms of PLGA (Table 3, Fig. 2). Additionally, a hydrogen atom from PLGA formed a conventional hydrogen bond with the side chain hydroxyl group of Ser488. These interactions, characterized by distances ranging from 2.05 to 2.74 Å, suggest strong and specific binding. Furthermore, multiple van der Waals interactions (e.g., Leu386, Leu406, Lys413, Phe487, Leu429, Leu452, Leu456, Arg484) were also observed, contributing to the overall stability of the PLGA–BSA complex. These interactions may have a cumulative effect, collectively suggesting a stable and specific binding mode between PLGA and BSA (Fig. 2).

Table 2. Binding energy scores of selected ligands docked to the target PLGA

| Ligands | Binding Energy Scores (kcal/mol) |
|---|---|
| Bovine Serum Albumin | -5.11 kcal/mol |
| Bovine Hemoglobin | -4.65 kcal/mol |
| Bovine $\alpha$2-macroglobulin | -3.93 kcal/mol |
| Integrin $\beta$2, Talin 1 | -4.97 kcal/mol |

Table 3. Molecular interactions between BSA and PLGA as predicted by docking analysis

| Interactions | Distance | Category | Type | From | From chemistry | To | To Chemistry |
|---|---|---|---|---|---|---|---|
| A:Asn390:HD22 - :PLGA:O | 2.48 | Hydrogen Bond | Conventional Hydrogen Bond | A:Asn390:HD22 | H-Donor | :PLGA:O | H-Acceptor |
| A:Arg409:HH21 - :PLGA:O | 2.05 | Hydrogen Bond | Conventional Hydrogen Bond | A:Arg409:HH21 | H-Donor | :PLGA:O | H-Acceptor |
| A:Ser488:HG - :PLGA:O | 2.74 | Hydrogen Bond | Conventional Hydrogen Bond | A:Ser488:HG | H-Donor | :PLGA:O | H-Acceptor |
| :PLGA:H - A:Ser488:OG | 2.12 | Hydrogen Bond | Conventional Hydrogen Bond | :PLGA:H | H-Donor | A:SER488:OG | H-Acceptor |

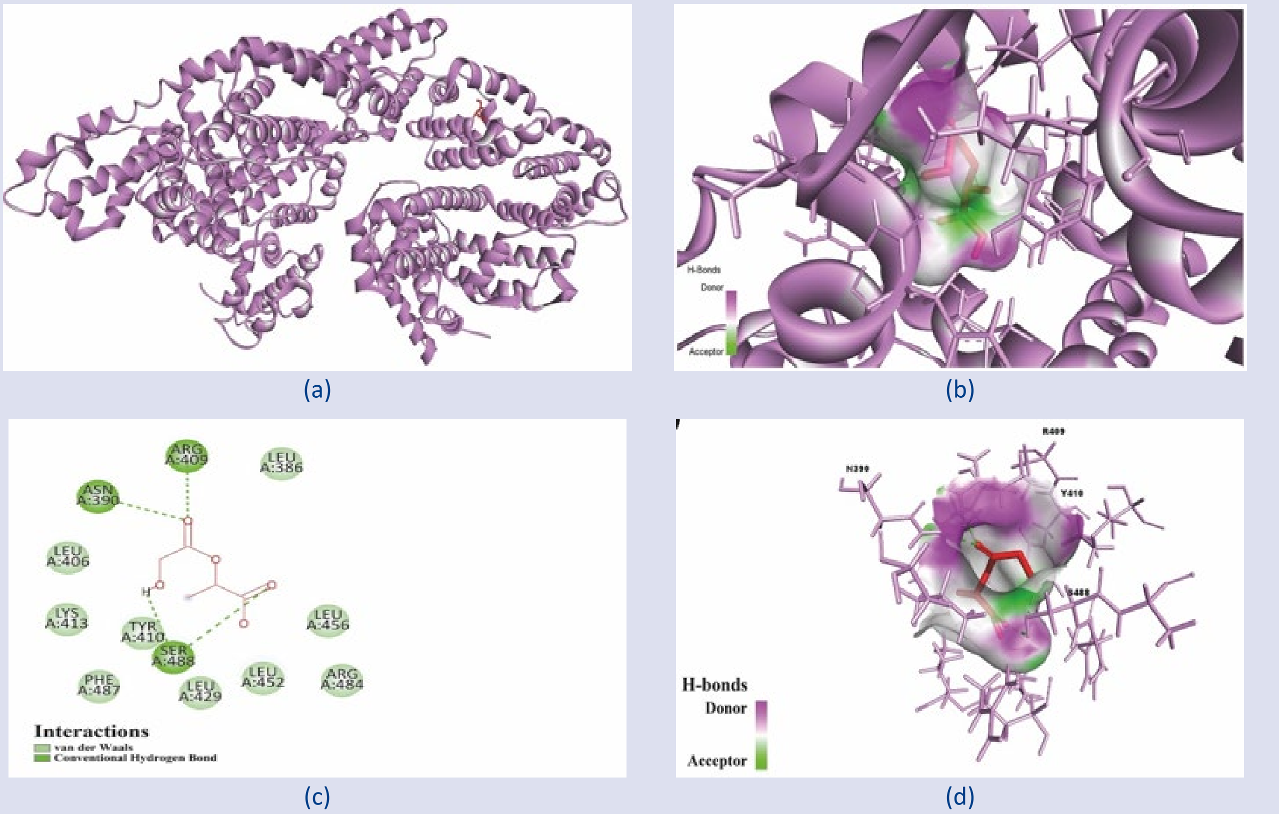



Figure 2. Docking interaction between PLGA and BSA. a) Three-dimensional (3D) representation of PLGA (red color) bound to the BSA (pink color). b) Zoom image of the binding pocket, represented by hydrogen surface. c) Two-dimensional (2D) interaction map displaying hydrogen bonds, carbon-hydrogen interactions, hydrophobic interactions, and van der Waals contacts between PLGA and specific amino acid residues of BSA. d) Surface representation of the binding pocket with specific interacting residues.

On the other hand, the ligand PLGA showed -4.65 kcal/mol binding affinity with the target protein, hemoglobin which had the second highest binding capacity after BSA protein among the serum proteins.

The binding analysis showed four hydrogen bonds that may contribute to the stability of the hemoglobin–PLGA complex. Conventional hydrogen bonds were found between the nitrogen atom of Phe70 and the oxygen atom of PLGA, as well as between hydrogen atoms of PLGA and the oxygen atoms of Phe102 and Val66 (Table 4, Fig. 3). Additionally, a carbon-hydrogen bond was identified between the side chain carbon of Ser69 and the oxygen atom of PLGA. Besides these polar interactions, several hydrophobic residues, including phenylalanine, valine, alanine and leucine (e.g., Phe84, Leu105, Leu140, Val136, Ala137, Val133, Gly106, Leu109, Leu67), were involved in van der Waals interactions, further stabilizing the complex.

Table 4. Molecular interactions between hemoglobin and PLGA as predicted by docking analysis

| Interactions | Distance | Category | Type | From | From chemistry | To | To Chemistry |
|---|---|---|---|---|---|---|---|
| D:Phe70:N - :PLGA:O | 3.10 | Hydrogen Bond | Conventional Hydrogen Bond | D:Phe70:N | H-Donor | :PLGA:O | H-Acceptor |
| :PLGA:H - D:Phe102:O | 3.00 | Hydrogen Bond | Conventional Hydrogen Bond | :PLGA:H | H-Donor | D:Phe102:O | H-Acceptor |
| :PLGA:H - D:Val66:O | 2.32 | Hydrogen Bond | Conventional Hydrogen Bond | :PLGA:H | H-Donor | D:Val66:O | H-Acceptor |
| D:Ser69:CB - :PLGA:O | 3.47 | Hydrogen Bond | Carbon Hydrogen Bond | D:Ser69:CB | H-Donor | :PLGA:O | H-Acceptor |

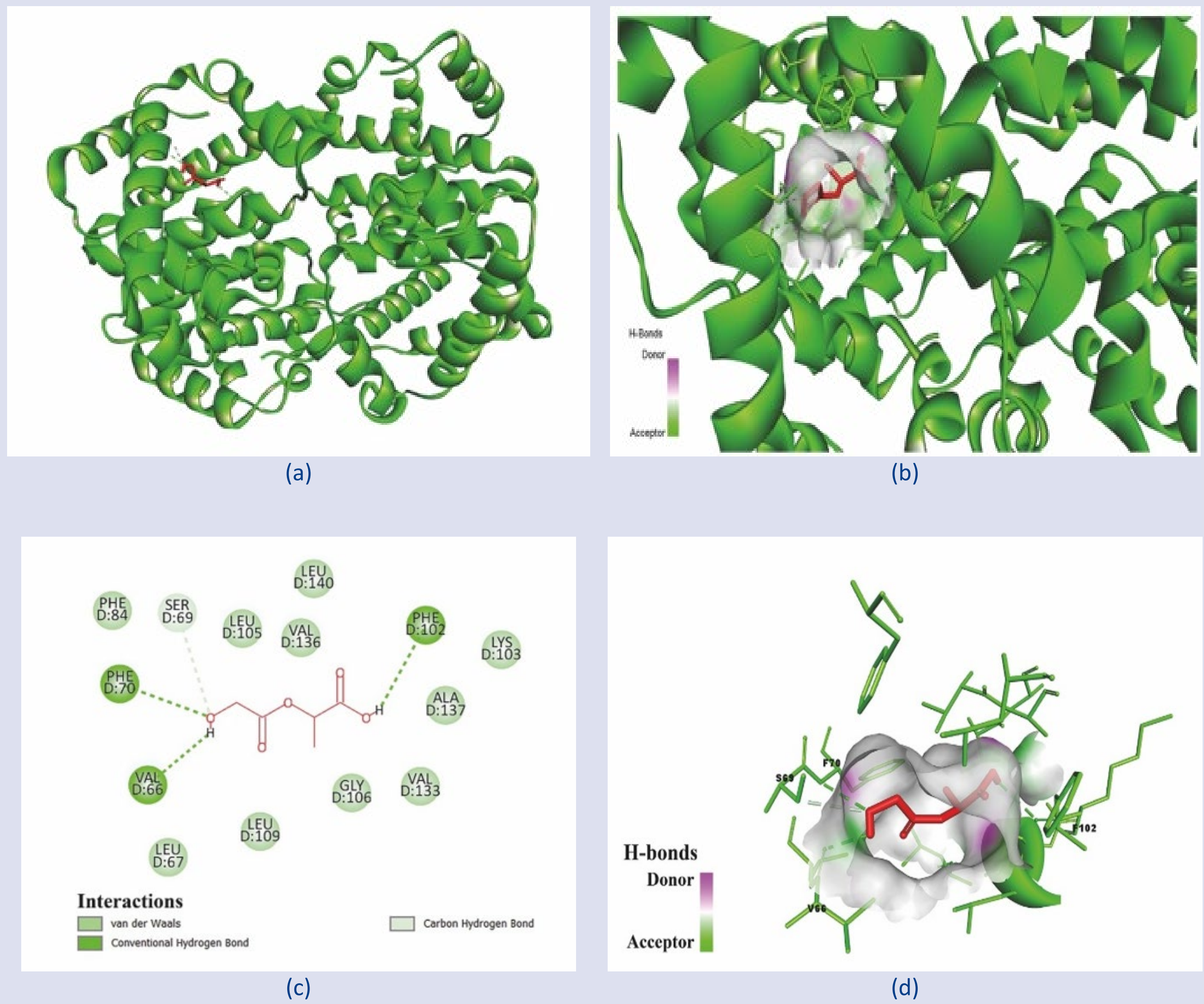



Figure 3. Docking interaction between PLGA and hemoglobin. a) Three-dimensional (3D) representation of PLGA (red color) bound to the Hemoglobin (green color). b) Zoom image of the binding pocket, represented by hydrogen surface. c) Two-dimensional (2D) interaction map displaying hydrogen bonds and van der Waals contacts between PLGA and specific amino acid residues of Hemoglobin. d) Surface representation of the binding pocket with specific interacting residues

For the last cell culture medium protein, α2-macroglobulin had the lowest binding capacity (Table 2). The interaction between PLGA and the bovine α2-macroglobulin was analyzed, revealing a binding energy of -3.93 kcal/mol, which suggests a weaker binding affinity compared to the hemoglobin-PLGA complex. Despite this lower binding affinity, the interaction between PLGA and bovine α2-macroglobulin involved three hydrogen bonds and multiple van der Waals interactions, contributing to the overall stability of the complex (Fig.4). Notably, Thr94 was found to be single residue forming three hydrogen bonds with PLGA, including one conventional hydrogen bond between the hydrogen atom of PLGA and the oxygen atom of the hydroxyl group (–OH) of Thr94, and two carbon hydrogen bonds where the carbon-bound hydrogens of Thr94' s side chain interact with the oxygen atoms of PLGA. This interaction highlights the importance of hydrophilic residue Thr94 in stabilizing the PLGA–α2-macroglobulin complex through hydrogen bonds. Additional residues such as Met63, Leu64, and Pro59 contributed to van der Waals interactions, further supporting the molecular interaction (Table 5, Fig. 4).

Table 5. Molecular interactions between bovine α2-macroglobulin and PLGA as predicted by docking analysis

| Name | Distance | Category | Type | From | From chemistry | To | To Chemistry |
|---|---|---|---|---|---|---|---|
| :PLGA:H - B:Thr94:O | 2.49 | Hydrogen Bond | Conventional Hydrogen Bond | :PLGA:H | H-Donor | B:Thr94:O | H-Acceptor |
| B:Thr94:CB - :PLGA:O | 3.34 | Hydrogen Bond | Carbon Hydrogen Bond | B:Thr94:CB | H-Donor | :PLGA:O | H-Acceptor |
| B:Thr94:CB - :PLGA:O | 3.49 | Hydrogen Bond | Carbon Hydrogen Bond | B:Thr94:CB | H-Donor | :PLGA:O | H-Acceptor |

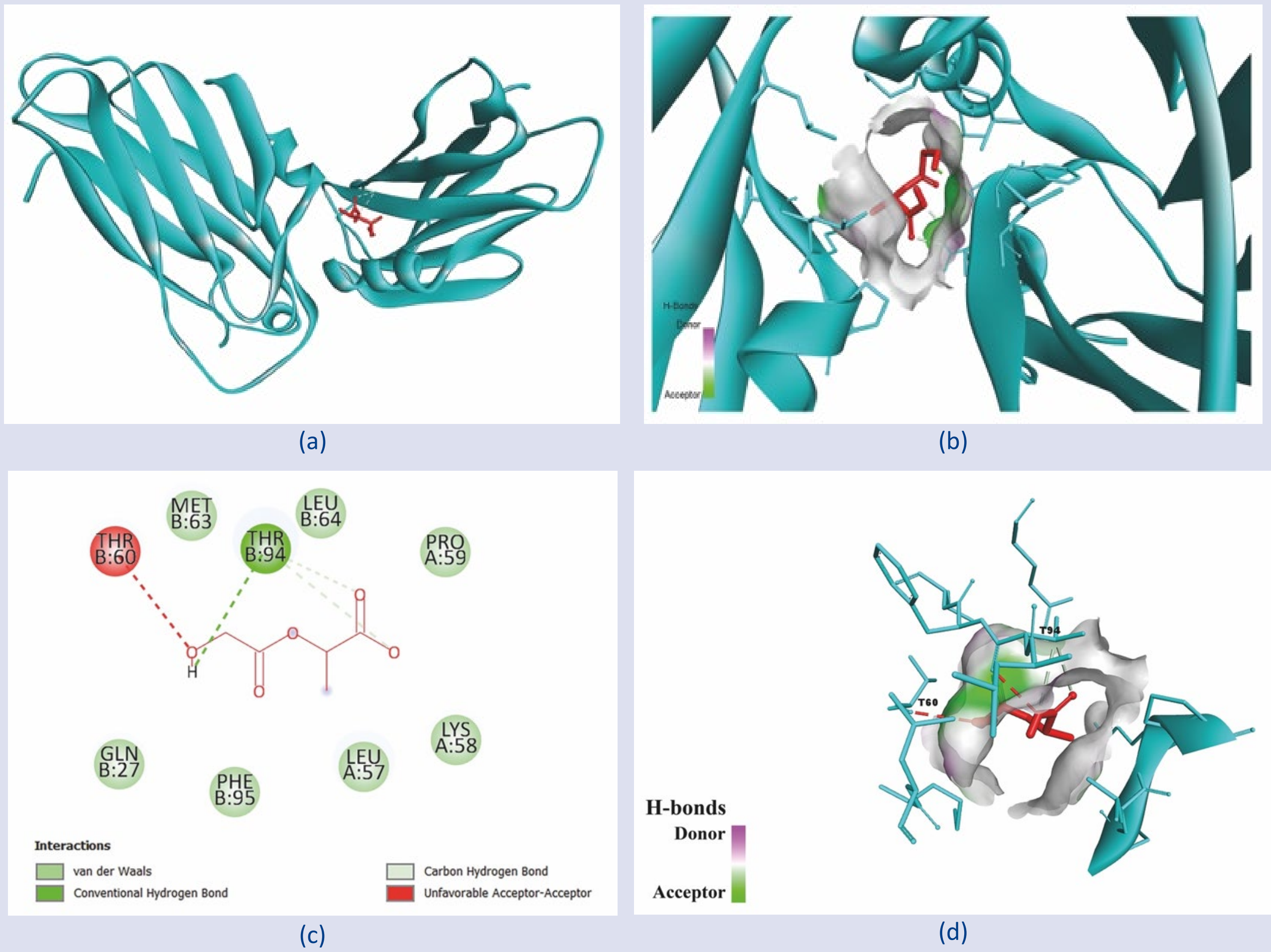



Figure 4. Docking interaction between PLGA and bovine α2-macroglobulin. a) Three-dimensional (3D) representation of PLGA (red color) bound to bovine α2-macroglobulin (cyan color). b) Zoom image of the binding pocket, represented by hydrogen surface. c) Two-dimensional (2D) interaction map displaying hydrogen bonds and van der Waals contacts between PLGA and specific amino acid residues of bovine α2-macroglobulin. d) Surface representation of the binding pocket with specific interacting residues.

The docking analysis between PLGA and integrin showed a strong binding affinity with a score of –4.97 kcal/mol, indicating a relatively strong binding affinity. Although bovine serum albumin (BSA) exhibited a slightly higher binding energy of –5.11 kcal/mol, the difference between their binding energies is minimal (ΔE = 0.15 kcal/mol), indicating that PLGA binds comparably well to both proteins. The interaction network analysis showed that PLGA forms conventional hydrogen bonds with integrin residues Thr307, Val310, and Ser311, alongside several van der Waals interactions involving Phe197, Asp222, His228, Phe312, Pro229, Gly309, Tyr308 (Table 6, Fig. 5).

Table 6. Molecular interactions between integrin and PLGA as predicted by docking analysis

| Name | Distance | Category | Type | From | From chemistry | To | To Chemistry |
|---|---|---|---|---|---|---|---|
| A:Val310:H - :PLGA:O | 2.42 | Hydrogen Bond | Conventional Hydrogen Bond | A:Val310:H | H-Donor | :PLGA:O | H-Acceptor |
| :PLGA:H - A:Ser311:OG | 2.01 | Hydrogen Bond | Conventional Hydrogen Bond | :PLGA:H | H-Donor | A:Ser311:OG | H-Acceptor |
| :PLGA:H - A:Thr307:O | 2.53 | Hydrogen Bond | Conventional Hydrogen Bond | :PLGA:H | H-Donor | A:Thr307:O | H-Acceptor |
| A:Ser311:HA - :PLGA:O | 2.77 | Hydrogen Bond | Carbon Hydrogen Bond | A:Ser311:HA | H-Donor | :PLGA:O | H-Acceptor |

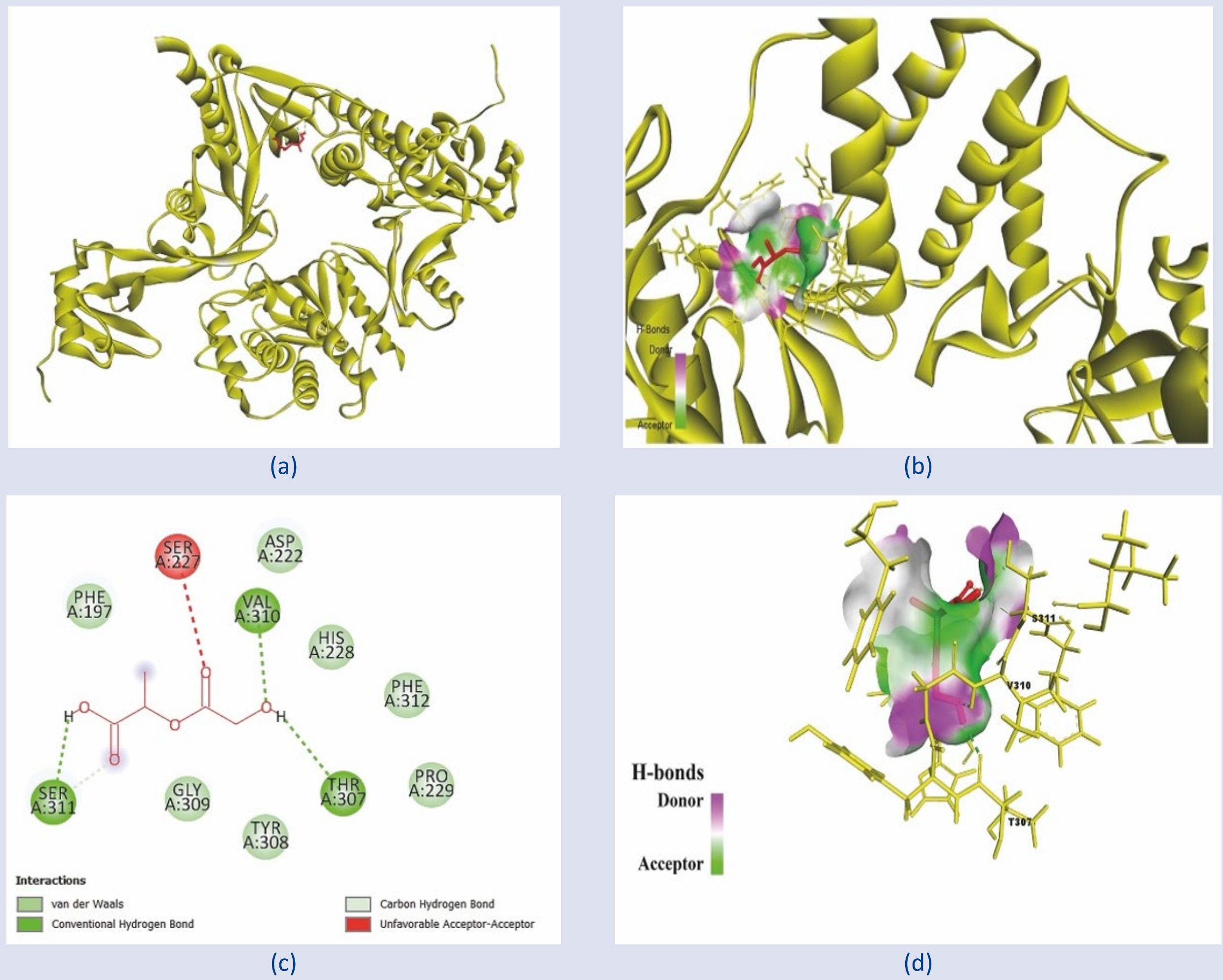



Figure 5. Docking interaction between PLGA and integrin β2. a) Three-dimensional (3D) representation of PLGA (red color) bound to the integrin β2 (gold color). b) Zoom image of the binding pocket, represented by hydrogen surface. c) Two-dimensional (2D) interaction map displaying hydrogen bonds and van der Waals contacts between PLGA and specific amino acid residues of Integrin. d) Surface representation of the binding pocket with specific interacting residues.

Among these results, it was investigated that all studied proteins could give interactions with ligand PLGA through different types of hydrogen bonds and van der Waals forces while integrin β2 and BSA indicated stronger and more robust and specific binding profiles. When considered as PLGA-based biomaterials, hydrophilic bonds as well as hydrophobic interactions can increase the overall binding capacity and residence time of proteins on the material surface [7]. On the other hand, these superior interactions are very critical for polymer surface properties to enhance cellular adhesion process. In this study, it was revealed that BSA exhibited the highest binding affinity to the PLGA surface. This finding suggests that BSA is most likely the first protein to adsorb to the biomaterial surface *in vitro*, and therefore, cells bind to the material surface through this protein layer rather than directly. This "protein corona" formation, which constitutes the first step in cell-material interactions, plays a decisive role in the nature of the cellular response. This highlights the critical role that the order of protein adsorption, a dynamic interface, plays in cellular sensing of the material surface. In tissues, when biomaterials are placed on the body, plasma proteins bind first; the type, amount, and conformation of these proteins directly influence the recognition potential of cellular receptors [23–27]. In this context, the strong binding capacity of BSA suggests that the initial microenvironment formed on the PLGA surface will serve as a biochemical signaling platform for cells. Cellular adaptation, proliferation, or differentiation on the surface may also be mediated by the ligands presented by this protein layer. Therefore, designing biomaterial surfaces considering the potential for interaction not only with target proteins but also with plasma proteins is important to optimize biocompatibility and functional performance.

On the other hand, integrin protein is one of the cellular surface adhesion molecules and plays a significant role in the formation of cell-cell and cell-ECM connections. As it was mentioned previously, before the cells adhere to the material surface, plasma proteins (especially BSA) from water and cell culture medium adsorb onto the material surface and then, the cell is expected to form an interaction to these surfaces [7]. The binding process involved the rapid formation of various hydrophilic bonds, indicating that enhancing surface hydrophilicity could improve protein binding efficacy. In our previous study, it was found that by fabricating nanophase topographies to the PLGA surface, the hydrophilic properties of the surface increased, and protein adsorption on the surfaces was higher and neuronal cells demonstrated better spreading [15]. Additionally, since PLGA surfaces with nanophase topographies indicated that not only increase plasma protein adsorption but also could enhance biologically active conformation of integrins like integrin $\beta$2 on adsorbed proteins. So, the computational results by molecular docking process confirmed these *in vitro* results. The results also were in-line with existing literature findings [8,28–31]. On the other hand, while BSA demonstrate comparatively robust binding to PLGA ligand, it has functioning role as a stabilizing molecule in early protein adsorption layers [10]. Additionally, hemoglobin and $\alpha$2-macroglobulin had the lower affinity and less specific interactions with PLGA ligand suggest that despite their abundance in serum containing culture medium, their effects on cell-material interactions are limited compared to others. These differences in interaction profiles, especially in binding distances are significant for evaluating and understanding the stability, specificity, and orientation of protein adsorption on material surfaces, as these factors are closely related to the initial protein recognition and the bioactivity of the materials.

To sum-up, these findings provide mechanistic insight into how PLGA and specific protein interactions at the molecular scale have been occurred. The evaluation of these findings emphasizes the significance of fabricating polymers and their surfaces to selectively engage proteins which participate in cell-ECM communication. By revealing key points and binding types that related with protein binding, molecular docking analysis serves as a strategic tool for giving information the molecular scale design of biomaterials in specifically neural and other types of tissue engineering and regenerative applications like other research areas [13,32–35].

## Conclusion

The results from the conducted molecular docking studies provided the significant information about which residues and bonds are participating and how effectively occurring interactions between the proteins, BSA, hemoglobin, $\alpha$2-macroglobulin and integrin $\beta$2 binding to the related material, PLGA ligand. Notably, both BSA and integrin β2 exhibited strong binding affinity to PLGA. Consistent with existing literature identifying serum proteins (for this study BSA) as the primary contributor to functional adhesion at the cell–material interface, our docking analysis also confirmed this, showing a favorable binding energy score. In contrast, weaker and fewer types of interactions were found for hemoglobin and $\alpha$2-macroglobulin suggesting their limited role for the cellular adhesions and related responses. All of these results indicate the critical role of molecular docking analysis to evaluate molecular recognition while designing and fabricating biomaterials for tissue engineering and regenerative medicine. For future studies, combining molecular docking analyses with molecular dynamics simulations could provide broader perspectives into how the binding process evolves over time and the thermodynamic stability of the interactions. Furthermore, strategies such as chemical modification of PLGA, surface functionalization, or copolymerization with other biocompatible polymers can optimize protein binding selectivity and cellular responses. Furthermore, integrating this molecular docking analysis with *in vitro* cell culture and, especially cellular adsorption studies will contribute to more predictable and controlled surface-biomolecule interactions in biomaterial design for the studies of tissue engineering and regenerative medicine.

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## Conflicts of Interest

There are no conflicts of interest in this work.

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