Engineering of macrophage targeted Punicalagin nanoparticles by computational modeling to alleviate methotrexate induced neutropenia

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Research Article

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Title: Engineering of macrophage targeted Punicalagin nanoparticles by computational modeling to alleviate methotrexate induced neutropenia

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Abstract

Punicalagin is the most bioactive polyphenols of pomegranate and has the potential to cure different ailments related to the CVS system. The current research work was envisioned to predict the targeting efficiency of punicalagin (PG) nanoparticles to the macrophages. For this, we select mannose decorated PLGA-punicalagin nanoparticles (Mn-PLGA-PG) and before formulation we predict the targeting efficiency of this nanocarrier by *in-silico* analysis. Authors initiated *in-silico* analysis on macrophage mannose receptor to be acquainted with the binding affinity. *In-silico* docking studies of macrophage mannose receptor and punicalagin showed binding interaction on its surface with a docking score of -4.00.PG interacts with hydrogen bonds to the charged residue ASP668 and GLY666 and polar residue GLN760 residue of Mn receptor. Mannose with a docking score of -5.811 and interacting with four hydrogen bonds to the mannose receptor of macrophage with two negatively charged residues GLU706, GLU719 also with two hydrophobic residues VAL716, PHE708 and in PLGA, it showed a -4.334-docking score. In trajectory analysis, the complex RMSD of macrophage while stabilizing the structure till 100ns, Mn receptor-PG found within the range of 4.6 Å. Initial fluctuation in RMSD noticed to 4.95 Åat 20ns which started stabilizing with timescale. In the total of 100ns, initially up to 40ns the PG (ligand) deviated to 1.2Å after 40ns, it is noted that the ligand RMSD was almost constant and started stabilizing and at 100ns it was 1.03Å. Findings depict that this nanocarrier could be a promising lead molecule to regulate the incidence of drug induced neutropenia.

Keywords: Punicalagin, Mannose, Nanoparticles, *In-silico* design, MD simulation, Docking Study

Introduction

The nanoparticulate system gained widespread use in the arena of chemotherapeutics and is currently involved in neurodegenerative, CVS, cancer, and other chronic ailments. The nanoparticulate drug delivery system represents a viable option that provides spatial and temporal controlled delivery of peptides, therapeutics, or other bio-actives [1]. Numerous researchers proved that the nanoparticles improved the treatment of cancer through sophisticated functionalization and their ability to accumulate within certain tumors [2]. Despite all this, several nanomedicines fail during clinical trials due to certain issues. One of them is a lack of understanding of nanoparticles design, or how design of the nanoparticles impacts their ability to cross transport barriers such as circulation in the blood stream, extravasation in tumor cells or transport into the tumor tissues, internalization in tumor tissue or release of active cargo in situ. Computational tools and multi-scale simulations allow us to design the nanoparticles or study their effect on biological transporter, the release of the drug, or targeting to specific receptors in biological scenario [3]. Currently, advancement in computational modeling and multi-scale simulations allow to predict a range of parameters those influenced nanoparticles in the biological scenario. This type of future pipelines enables us to provide with general design principles which when combined with patient-specific data provides the information related to personalized treatment and care. In addition, utilization of *in-silico* analysis can minimize the expenses involved in more conventional trial and error procedures in the laboratory specially when pooled with latest machine learning techniques such as active learning [4].

Copious reports available in scientific databases reported that there are many computational methods and models that predict diverse phases of tumor initiation, growth and interaction of nanoparticles within the body and tumor. During the course of tumor treatment, certain medications in chemotherapy were provided to the patient to improve their quality of life. But at a certain point, these medications offer some side effects and that impact the health status of the patient. One such anticancer drug, methotrexate cause several side effects but the most prominent side effect encountered is Neutropenia i.e lowering down the level of neutrophils in blood circulation [5] Methotrexate is more commonly prescribed for the treatment of Rheumatoid arthritis as DMARDs and often accompanied with hematological toxicities (thrombocytopenia, leucopenia, pancytopenia, megaloblastic anemia), even at small doses [6]. This is a serious concern pertaining to chemotherapeutic patients and as well as to autoimmune RA patients. Therefore, stepping into this, filgrastim is frequently co-prescribed with chemotherapeutic drugs that are at risk of developing neutropenic conditions [7]. Looking more into the solution segment, we came across punicalagin, a phytoconstituent of pomegranate is also effective in healing neutropenic conditions [8]. Punicalagin (PG) is a phenolic compound and reported to exert numerous beneficial effects in the treatment of certain disorders such as cancer [9], inflammatory disorders [10], nephroprotective [11], cardiovascular diseases, scavenge oxidative free radicals, reduces the risk of atherosclerosis [12] and certain other chronic ailments.

In the current research work, we select mannose decorated PLGA punicalagin (Mn-PLGA-PG) nanoparticles to alleviate methotrexate-induced neutropenic settings. The selection of this nanocarrier is based on the ideology that neutropenia occurs in the bone marrow and therefore, to counteract this condition, we have to target our punicalagin molecule extensively to the bone marrow site. Bone marrow macrophages have mannose receptors present on their

surface in abundance and if we decorate the PG nanocarriers with mannose then they bind extensively to bone marrow macrophages. On extensive literature search and to the best of authors' information, none of the studies describe the targeting efficiency of Mn-PLGA-PG nanocarriers to bone marrow, responsible for alleviating methotrexate-induced neutropenia. Therefore, in our proposed work, we explore the design of targeted nanocarrier to bone marrow and secondly whether the proposed nanocarrier is efficient in delivering the PG molecule to its site of action by molecular docking and dynamics simulation studies.

Methodology

Protein and ligand preparation

The presence of mannose receptor site on macrophages is already elucidated by researchers, therefore from scientific databases, for macrophage mannose receptor we have taken 1EGI PDB ID, and removed chain A as it is incomplete and the most extended chain B was then taken further for the studies [13]. After fixation of the problem with CA (802), we have removed the water beyond 3.0 Å. Also, the solvents were removed during the analysis. As far as ligands are concerned we have taken Punicalagin (HMDB05795), Mannose (18950), and poly(lactic-co-glycolic acid), or PLGA (23111554) to prepared in 3D SDF format for the molecular docking studies.

Molecular Docking studies

A molecular docking study was conducted to investigate if ligand (PG) binds to the macrophage receptor and the behavior of other carriers' mannose and PLGA. We performed molecular docking studies by Autodock (http://autodock.scripps.edu/) and MGL tools (http://mgltools.scripps.edu/) [14]. Grid file generated around the complete chain B for blind docking studies as it is not bound to any native ligand. Further, the academic version of Schrodinger Maestro (https://www.schrodinger.com/freemaestro/www.deshawresearch.com) [15] and PyMol (https://pymol.org/2/) [16] used for the visualization of interaction and bonding analysis of protein-ligand complexes.

Molecular Dynamics simulations

The dynamic behavior of protein-ligand complex in simulated physiological conditions is studied with the aid of molecular dynamic (MD) simulation studies.MD simulations of the macrophages mannose receptor-ligand complex were performed using the academic version of Desmond application available with Schrodinger maestro (v 2020-4) [15,16] The macrophage mannose receptor-punicalagin (2337 atoms) solvated in a 10 × 10 × 10 Å orthorhombic periodic box built with TIP3P water molecules. The whole system was neutralized by adding 4Na+ counter ions and the solvated system was energy minimized and position restrained with OPLS3e force field [17]. For macrophage mannose receptor-mannose (2258 atoms) 1Na+ and macrophage mannose receptor-PLGA (2251) 2Na+ added to neutralize the system. Both systems were also solvated in a 10 × 10 × 10 Å orthorhombic periodic box built with TIP3P water molecules and minimized with the same OPLS3e forcefield. Ions and salt placement within 20 Å excluded in all systems. Further, 100 ns of molecular dynamics simulation was carried out at 1 atm pressure and temperature of 300 K including the implementation of NPT ensemble with a recording interval of 100 ps resulting in 1000 reading frames for each complex separately to check and evaluate the behavior. In the end, various parameters

of Molecular Dynamics simulation study such as Root mean square fluctuation (RMSF), Root mean square deviation (RMSD), secondary structure element (SSE) analysis, protein-ligand (PL) contacts; ligand binding site analysis, etc. were analyzed to check the structural fluctuations, compactness, stability and protein-ligand interactions within solvated system [18,19].

Results

Interaction analysis

In-silico docking studies of macrophage mannose receptor and punicalagin showed binding interaction on its surface with a docking score of -4.00. In Figure 1A, we have demonstrated the interaction of punicalagin with the macrophages mannose receptors. Punicalagin interacts with hydrogen bonds to the charged residue ASP668 and GLY666 and polar residue GLN760 residue. In figure 1B we have discovered Mannose with a docking score of -5.811 and interacting with four hydrogen bonds to the mannose receptor of macrophage with two negatively charged residues GLU706, GLU719 also with two hydrophobic residues VAL716, and PHE708. In PLGA, it showed a -4.334 docking score and interacts with three hydrogen bonds (Figure 1C), LYS739 (positively charged), HIS692 (polar), and LEU694 (hydrophobic). Descriptive table (Table 1) with molecular docking score and the generated energy with respective ligands (PG, Mannose, and PLGA) provide insight into the interaction analysis.

Molecular dynamics simulation

MD simulation provides information about the receptor-ligand complex with the timescale, so we performed the MD simulation for 100ns on all 3 complexes generated through molecular docking. Molecular Dynamic simulations of the protein-ligand complex performed using Desmond 6.1 (Maestro v12.3), and we have analyzed the trajectory files for Root mean square deviation (RMSD), Root means square fluctuation (RMSF), protein-ligand interactions, etc. Root mean square deviation (RMSD) describes the average change in displacement of an atom in a specific molecular level conformation with its referential conformation data. In trajectory analysis, the complex RMSD of macrophage mannose receptor-punicalagin found within the range of 4.6Å while stabilizing the structure for 100ns of simulation. Initially, up to 20ns the RMSD value of the complex was 4.65 Å. RMSD values fluctuated but started stabilizing after 20ns which then increased the maximum at 4.95 Å (Figure 2A). In the total of 100ns, initially up to 40ns the punicalagin (ligand) deviated to 1.2Å after 40ns, it is noted that the ligand RMSD was almost constant and started stabilizing and at 100ns it was 1.03Å. This depicts that the complex structure does not deviate to a great extent after 40ns and started stabilizing afterward. However, the punicalagin fit on the receptor has quite deviated. We monitored and examined the backbone atoms for stability, compactness and to know the structural fluctuations in the interaction of protein-ligand complex within solvated system. The Root Mean Square Fluctuation (RMSF) is helping us to characterize the local changes along with the protein chain and been calculated throughout the dynamics18. It alludes to the Root mean square displacement of apiece residue for a frame conformation related to the average conformity, which is utilized to resolve the flexibility of protein's regions. In an RMSF plot, the peak indicates the regions (residues) of the protein fluctuates most during the simulation, while the fall in RMSF plot represent less conformational change. The analysis revealed that the RMSF plot (Figure 2B) displays minimal

fluctuations in the protein structure while comparing to the PDB. We observed that the protein-ligand complex displayed lower flexibility, and the RMSF plot showed fluctuations in some regions of the protein residues. A total of 54 time periods punicalagin interacted with the protein structure during the simulation. While analyzing the residue interactions during the simulation period, it was observed negatively charged residues like ASP741, GLU 677 interacts with hydrogen bonds, also positively charged residues like LYS763, ARG663, LYS739, and LYS693 interact within. A total of 10 water molecules are involved during the simulative interactions (Figure 2C). Polar residues like HIS692, GLN760, GLN762, and hydrophobic residues PRO742 and TYR691 participated in-water interaction.

In macrophages mannose receptor-mannose complex trajectory analysis, the complex RMSD of macrophage mannose receptor-mannose found within the range of 4.6Å while stabilizing the structure for 100ns of simulation. Initially, up to 20ns the RMSD value of the complex was 4.65 Å. RMSD values fluctuated but started stabilizing after 20ns which then increased the maximum at 4.65 Å (Figure 3A). In the total of 100ns, it is noted that the mannose RMSD was almost constant and at maximum, it shows 0.60Å deviation and at 100 ns it comes to 0.14Å. This depicts that the complex structure does not deviate much after 40ns and started stabilizing afterward. However, the mannose fit on the receptor deviated. The peak in the RMSF plots indicates the most fluctuation in protein's regions (residues) during the simulation, while the fall in RMSF plots represent less conformational changes. The analysis revealed that the RMSF plot (Figure 3B) displays a minimal fluctuation in the protein structures and ends at 2.22 Å. A total of 82 time periods mannose interacted (green color) with the protein structure during the simulation. While analyzing the residue interactions during the simulation period, it was observed negatively charged residues GLU725 interacts with hydrogen bond and a total of 2 water molecules are involved during the simulative interactions (Figure 3C). Polar residues like ASN728, THR709 interacted with water and OH groups to properly stabilize the complex. In macrophages mannose receptor-PLGA complex trajectory analysis, the complex RMSD of macrophage mannose receptor-PLGA found within the range of 4.6Å while stabilizing the structure for 100ns of simulation. Initially, up to 20ns the RMSD value of the complex was 4.65 Å. RMSD values fluctuated but started stabilizing after 20ns which then increased the maximum at 4.95 Å (Figure 4A). In the total of 100ns, it is noted that the PLGA RMSD was almost constant at 100 ns it comes to 0.91Å. This detonates that the complex structure has not deviated much after 40ns and started stabilizing afterward. However, the PLGA fit on the receptor deviated only 2.46Å at 69ns. The analysis also suggests that the RMSF plot (Figure 4B) displays minimal fluctuations in the protein structures and ends at 1.77 Å. A total of 57 time periods PLGA interacted (green color) with the protein structure during the simulation. While analyzing the residue interactions during the simulation period, it was observed positively charged residues LYS693, LYS652, LYS649 are directly interacting with the PLGA with hydrogen bond and a total of 4 water molecules are involved during the simulative interactions (Figure 4C). Only single Polar residues ASN756 interacted with a hydrogen bond to the O-. Also, one hydrophobic residue LEU694 participates in the interaction.

Discussion

In-silico analyses have highlighted the best possible design for bone marrow targeted nanoparticles. In our scientific investigation, we use punicalagin, mannose, and PLGA to perform the molecular docking, and to ensure the complex behavior we have executed the molecular 100ns dynamics simulation on the same generated complexes.

The targeted nanoparticle delivery system offers certain advantages in terms of site-specific delivery of cargo. This present work is based on the idea of an active targeting approach in which a ligand molecule is decorated on nanoparticles encapsulated with drug moiety [1]. These types of targeted nanocarriers mediate receptor-oriented endocytosis process and thereby deliver the drug (PG) at bone marrow (site of action). These targeted delivery systems enable the cargo to release at the specific site and to avoid their peripheral deposition. Overcoming nanoparticle transport barriers, tissue penetration or release of cargo at specific site is of utmost importance while formulating nanocarrier. Computational *in-silico* analysis paved a fast and systematic exploration of nanoparticles design to deliver the therapeutic drug at site of action [3,4]. General principles and guidelines extracted from such types of tools and techniques helps in designing effective treatments [20]. Study conducted by Gupta and Rai, 2018 reported that the permeation of nanoparticles through skin layers is predicted with the help of constrained and unconstrained molecular dynamics simulations [21]. This study in corroboration to our research work in which targeting efficiency was investigated with target receptors. Certain other research encountered that uses machine learning techniques for predicting parameters of nanoparticles. Yan 2019 et al conducted in-silico profiling of nanoparticles using universal nanodescriptors [22]. Lunnoo et al 2019 reported in-silico study of gold nanoparticle uptake in mammalian cell and predict nanoparticle parameters such as size, shape, surface charge and aggregation [23]. Certain elucidation can be provided to tailor nanoparticles and designing them in accordance to patient needs such as personalized medicine. Constructing useful *in-silico* tools will require close validation with *in-vitro* and *in-vivo* results. Recently in this pandemic era, Weiss et al., 2020 reviewed the nanotechnology-based approaches against COVID-19 pandemic [24]. Qu et al 2020 described the atomistic simulations between nanoparticles and lipid bilayers [25]. Stillman et al 2020 describe numerous methods of in-silico modeling for cancer nanomedicines [26]. Similarly, Casalin et al., 2019 described molecular modeling for nanomaterials, their challenges and their perspectives are also discussed in detail [27]. The overarching aim to design bone marrow macrophage targeted nanoparticles of punicalagin which accounts to treat chemotherapeutic drug-induced neutropenia. To become effective, nanoparticles design requires an organized method to prototyping. *In-silico* modeling has currently advanced to be used as an effective tool that minimizes expensive trial-error procedures. Although such modeling does not exist in isolation, and therefore collaboration between experimentalists, mathematical modelers and clinicians will be required to inform the preeminent transfer of knowledge. Initially as in first step, this methodology will help in identifying guidelines for design of suitable nanoparticles. We envisage a pipeline where the theoretical predictions are verified against the clinical effects and then returned to inform about the future simulations [20]. Moving further to our research, the molecular docking and MD simulation studies predict the targeting efficiency of mannose decorated PLGA-punicalagin nanoparticles (Mn-PLGA-PG). The molecular docking analysis provided us with a good docking score with all 3 compounds, Punicalagin (drug candidate) and other two biodegradable

nanocarriers bounded to the surface of macrophages mannose receptor. MD simulations were carried out for the duration of 100ns to analyze the compactness, fluctuations, residue interactions and most important protein-ligand stability. In the presence of the ligand, proteins 'stability increased due to presence of proper bonding coordination. Protein RMSD was almost the same for all ligands although the ligands RMSD quite varies, though all were below 1.5 Å. However, ligands fit on protein quite deviated. RMSD of ligand fit on protein starts stabilizing with timescale. We noticed the presence of significant hydrogen bonds, water bridges and hydrophobic interactions too during the simulation period. Also, there were a sufficient number of interactions showed by all complexes during the simulation timescale. Findings depict that the identified complex (Mn-PG) could be a potential lead candidate to target the mannose receptor present on the surface of bone marrow macrophages by interacting at the binding pocket. These simulation studies thereby enable us to predict the design of nanoparticles in biological settings [22].

The method of employing *in-silico* tools to predict the targeting efficiency prior to any experimental study is of utmost importance to the pharmaceutical industry. Molecular modeling techniques such as molecular dynamics, simulation predict the drug affinity, binding energy for polymer matrix PLGA. This embodies drug loading and drug targeting in the nanocarriers can be estimated and that will save valuable time and resources to the experimentalists.

Conclusion

The findings suggest that the engineering of NPs with the aid of computational tools and techniques helps in reducing the time and cost associated with their design, development, and deployment. This could lead to the development of an efficient carrier system for punicalagin with a macrophage targeting approach. In our futuristic work, we synthesize this nanocarrier in laboratory settings and evaluate its effect in the biological scenario.

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Conflict of Interest

There was no conflict of interest among the corresponding author and co-authors.

Authors Contribution

All authors contributed equally.

Availability of Data

Manuscript has no associated data.

Ethics approval

Ethics approval in not required.

Abbreviations

FRS: Free radical Scavenging; CVS: Cardiovascular system; Mn- Mannose; PLGA- poly(lactic) glycolic acid; RMSD- Root means square Deviation; PDB- Protein databank; RMSF- Root Mean Square Fluctuation; MD- Molecular Dynamic; PG-Punicalagin

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Figure legends

Figure 1. Docked ligand interaction diagram of the macrophage mannose receptor site and **1A.** Punicalagin with a docking score of -4.00, **1B.** Mannose with docking score -5.811, **1C.** PLGA with docking score -4.334.

Figure 2A. Root means square Deviation (RMSD) of macrophages mannose receptor and punicalagin after the initial RMSD values were stabilized. This plot shows RMSD values for macrophages mannose receptor on the left Y-axis, whereas for punicalagin, these values are indicated on the right Y-axis. The RMSD graph for the c-alpha is shown in blue color, ligand fit on ligand in pink color, and for punicalagin fit on macrophages mannose receptor in red color. **2B.** RMSF macrophage mannose receptor backbone and punicalagin complex, red color shows the B factor means the PDB and green color means the interaction of the punicalagin to the macrophage mannose receptor with timescale. **2C**. Macrophage mannose receptor-punicalagin interaction during the molecular dynamics simulation.

Figure 3A. Root means square Deviation (RMSD) of macrophages mannose receptor and mannose after the initial RMSD values were stabilized. This plot shows RMSD values for macrophages mannose receptor on the left Y-axis, whereas for mannose, these values are indicated on the right Y-axis. The RMSD graph for the c-alpha is shown in blue color, ligand fit on ligand in pink color,and for mannose fit on macrophages mannose receptor in red color. **3B.** RMSF macrophage mannose receptor backbone and mannose complex, red color shows the B factor means the PDB and green color means the interaction of the mannose to the macrophage mannose receptor with timescale. **3C**. Macrophage mannose receptor-mannose interaction during the molecular dynamics simulation.

Figure 4A. Root means square Deviation (RMSD) of macrophages mannose receptor and PLGA after the initial RMSD values were stabilized. This plot shows RMSD values for macrophages mannose receptors on the left Y-axis, whereas for PLGA, these values are indicated on the right Y-axis. The RMSD graph for the c-alpha is shown in blue color, ligand fit on ligand in pink color, and for PLGA fit on macrophages mannose receptor in red color. **4B.** RMSF macrophage mannose receptor backbone and PLGA complex, red color shows the B factor means the PDB and green color means the interaction of the PLGA to the macrophage mannose receptor with timescale. **4C**. Macrophage mannose receptor-PLGA interaction during the molecular dynamics simulation.

Table:

Table 1: Molecular docking score and the generated energy with respective ligands.

S.No	**Ligand**	**Docking Score**	**Energy**
1.	Punicalagin	-4.00	-45.762
2.	Mannose	-5.811	-27.205
3.	PLGA	-4.334	-24.163

Figure 1A

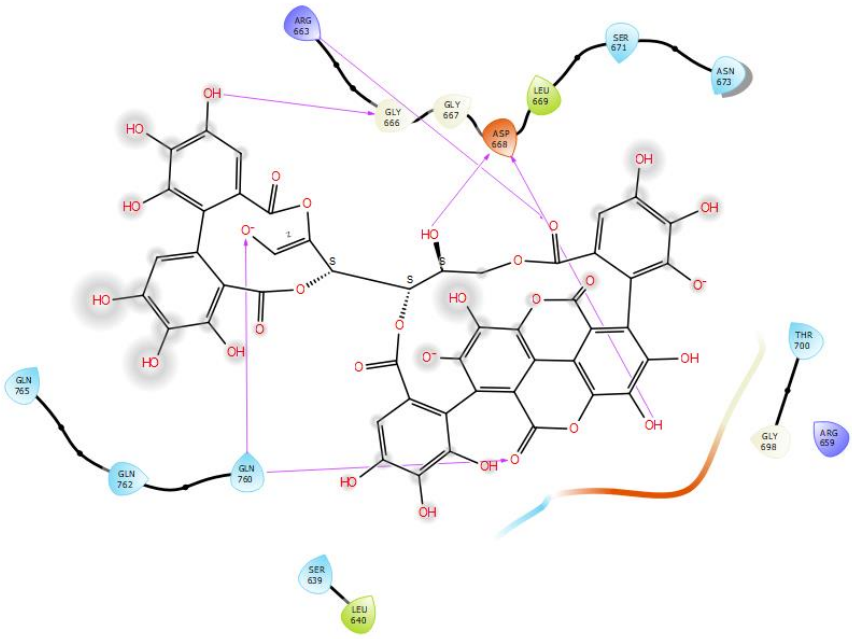


Figure 1B

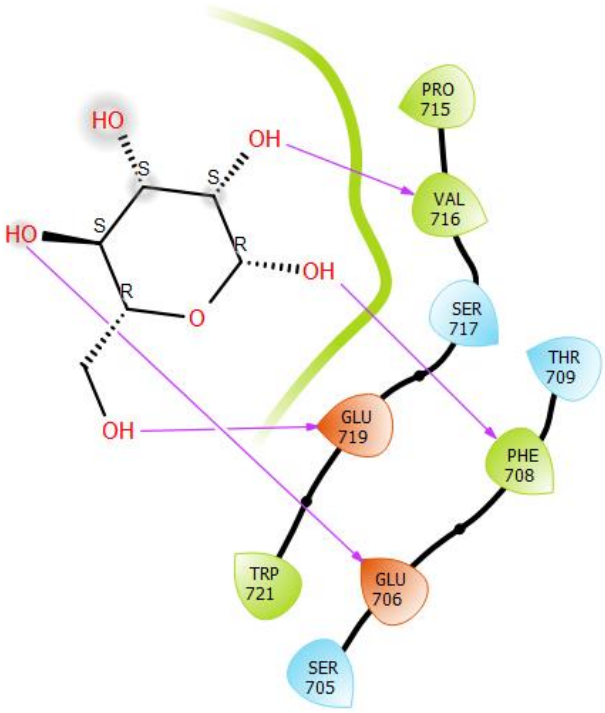


Figure 1C

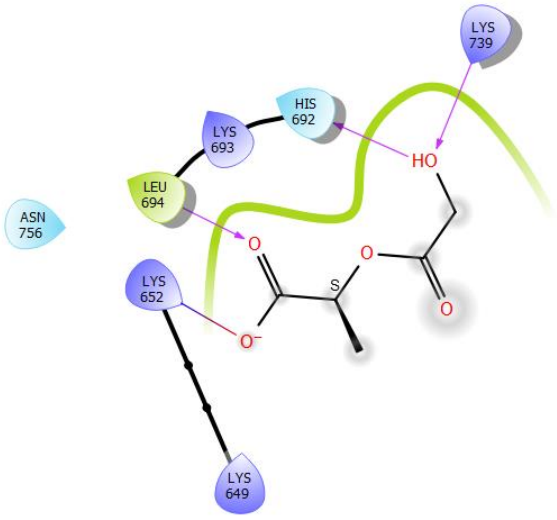


Figure 2A

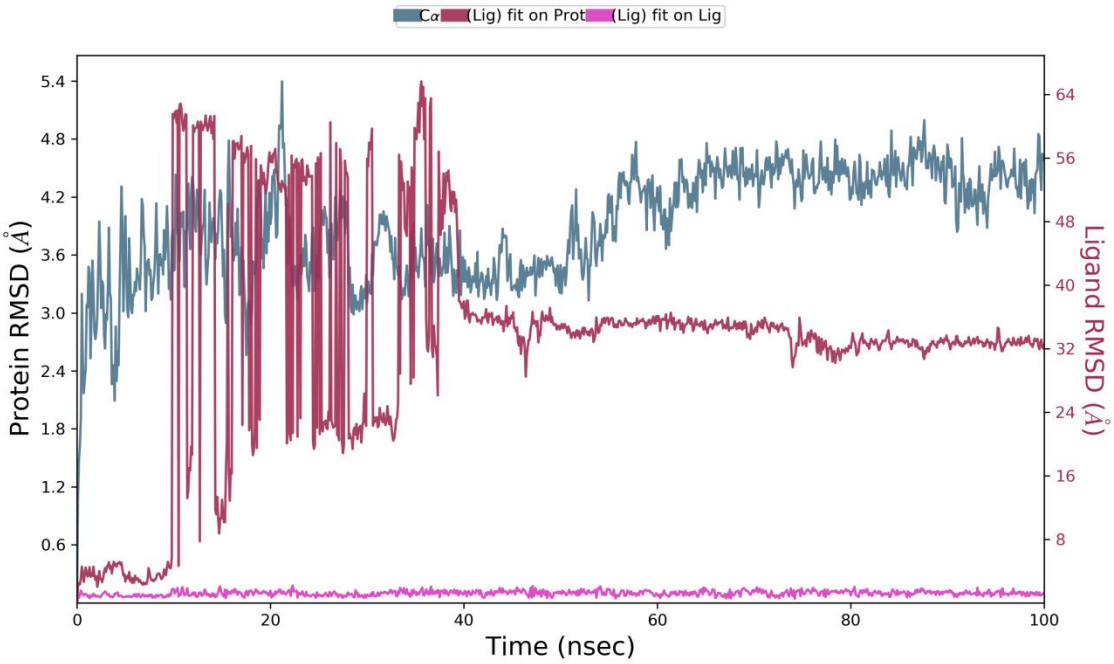


Figure 2B

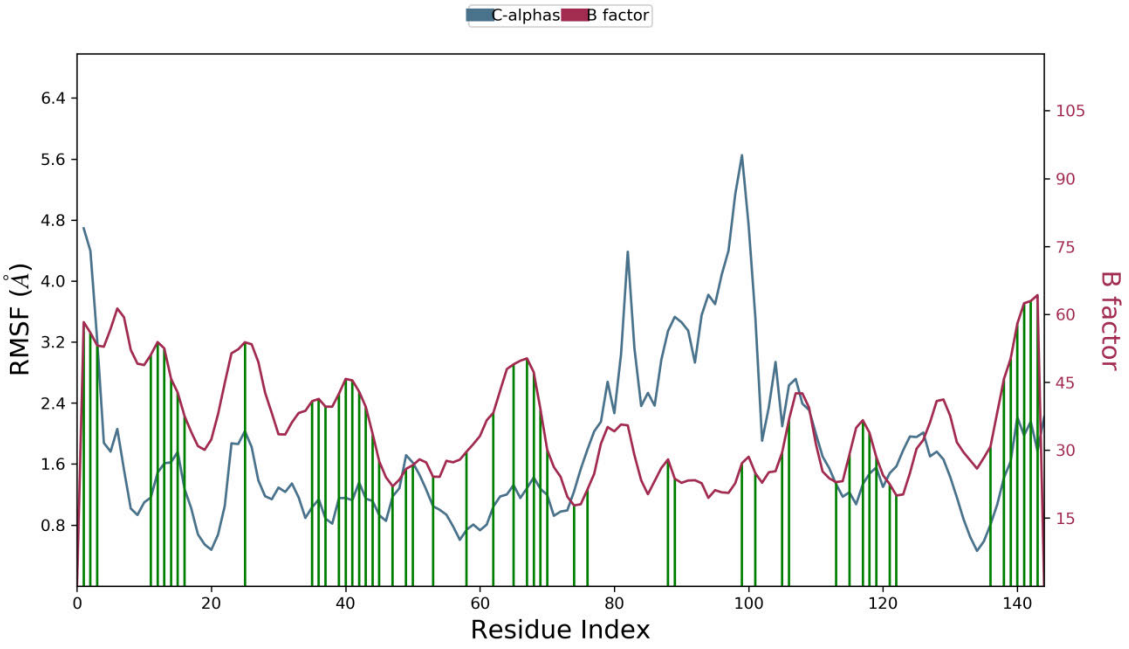


Figure 2C

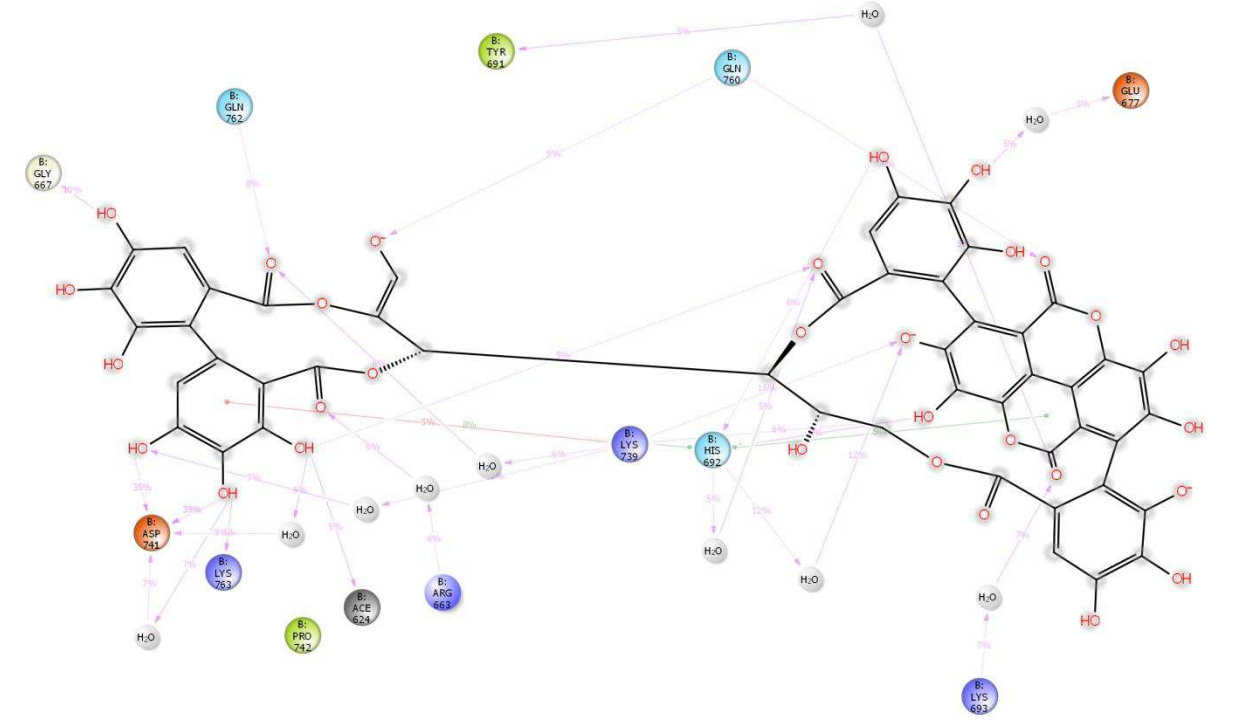


Figure 3A

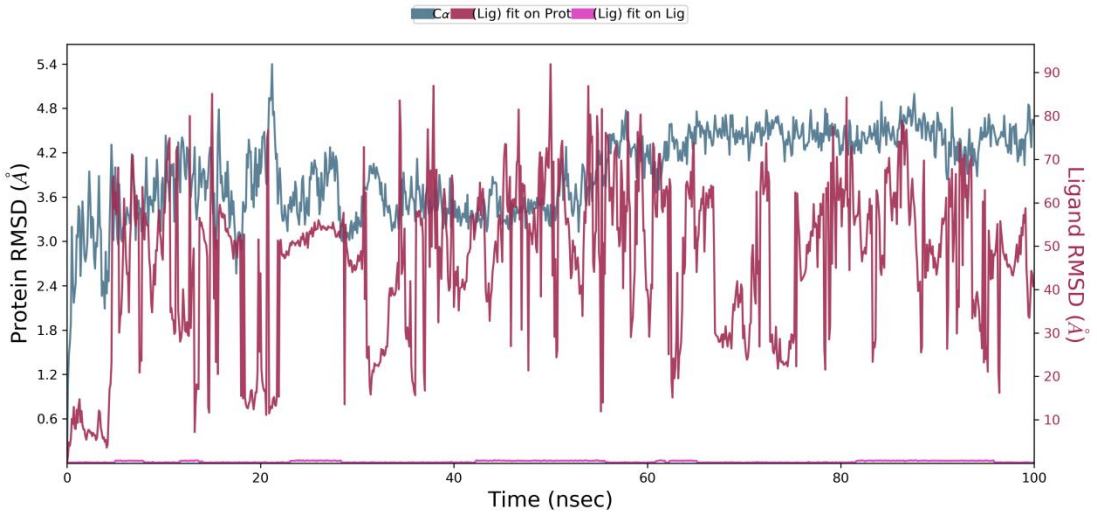


Figure 3B

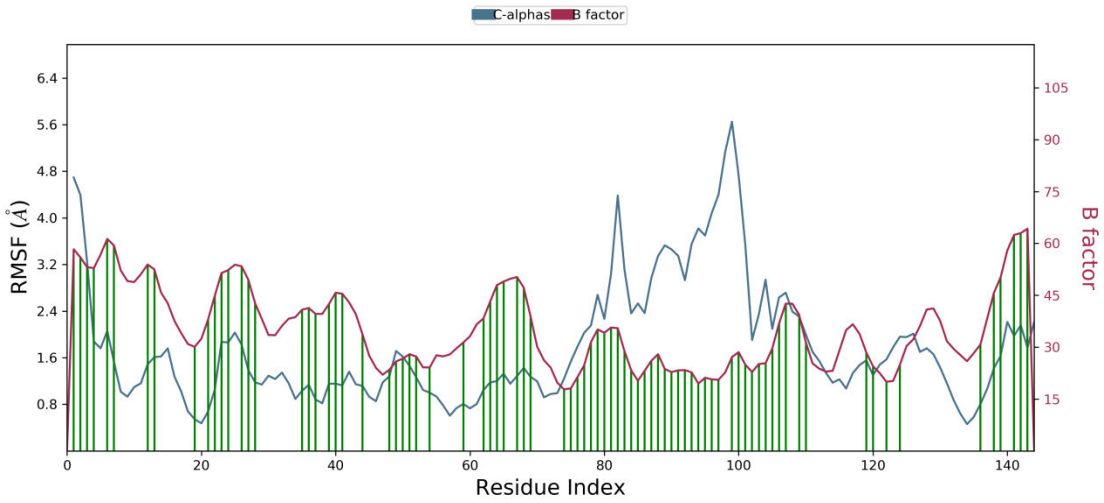


Figure 3C

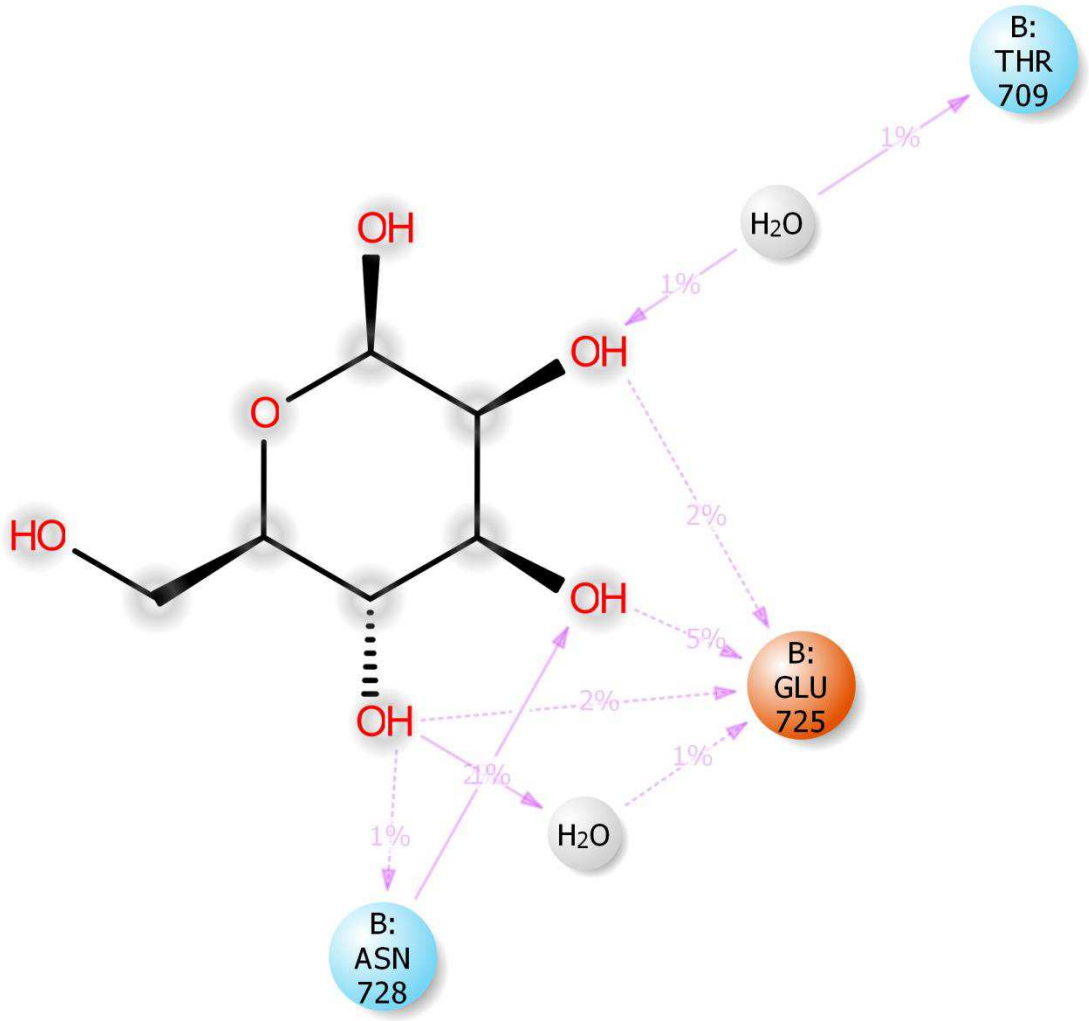


Figure 4A

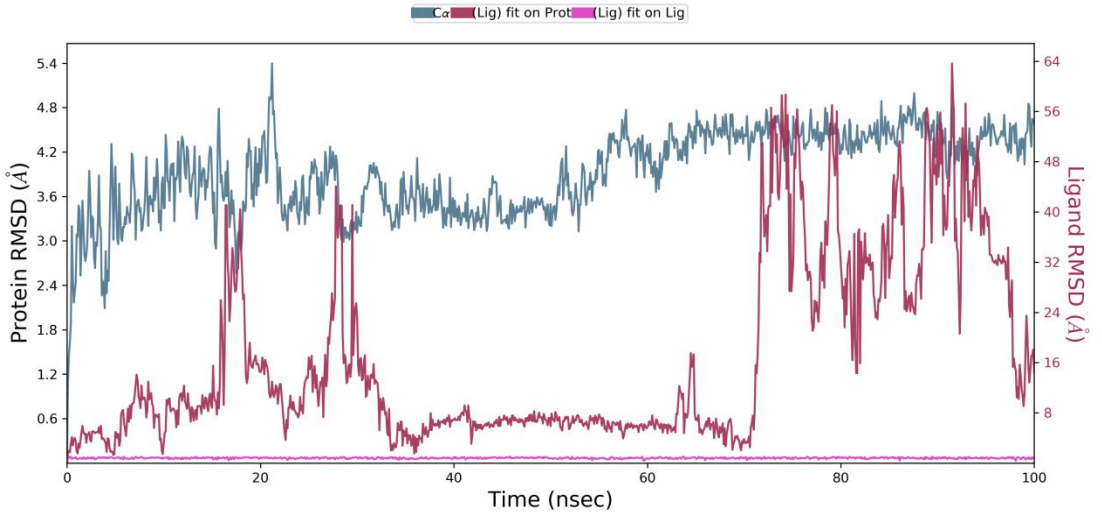


Figure 4B

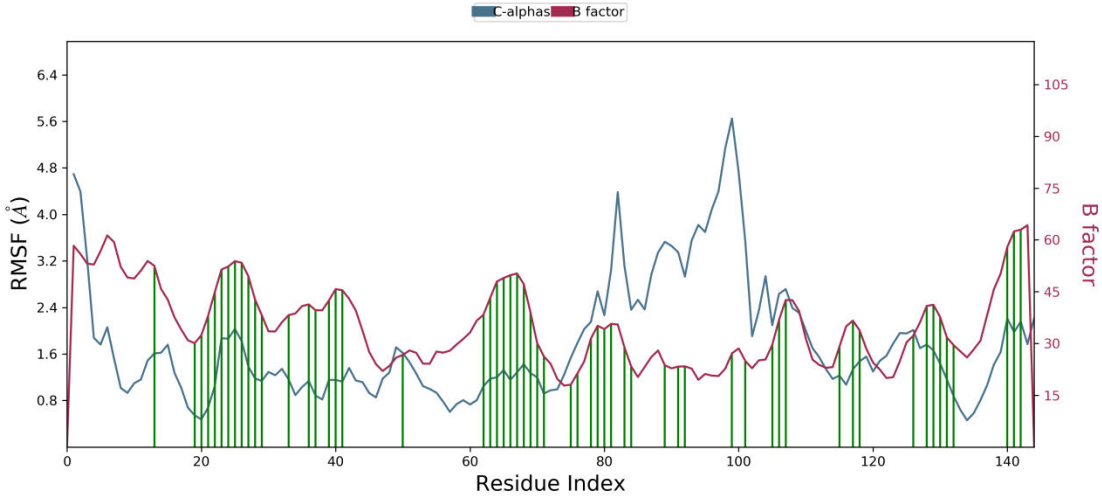
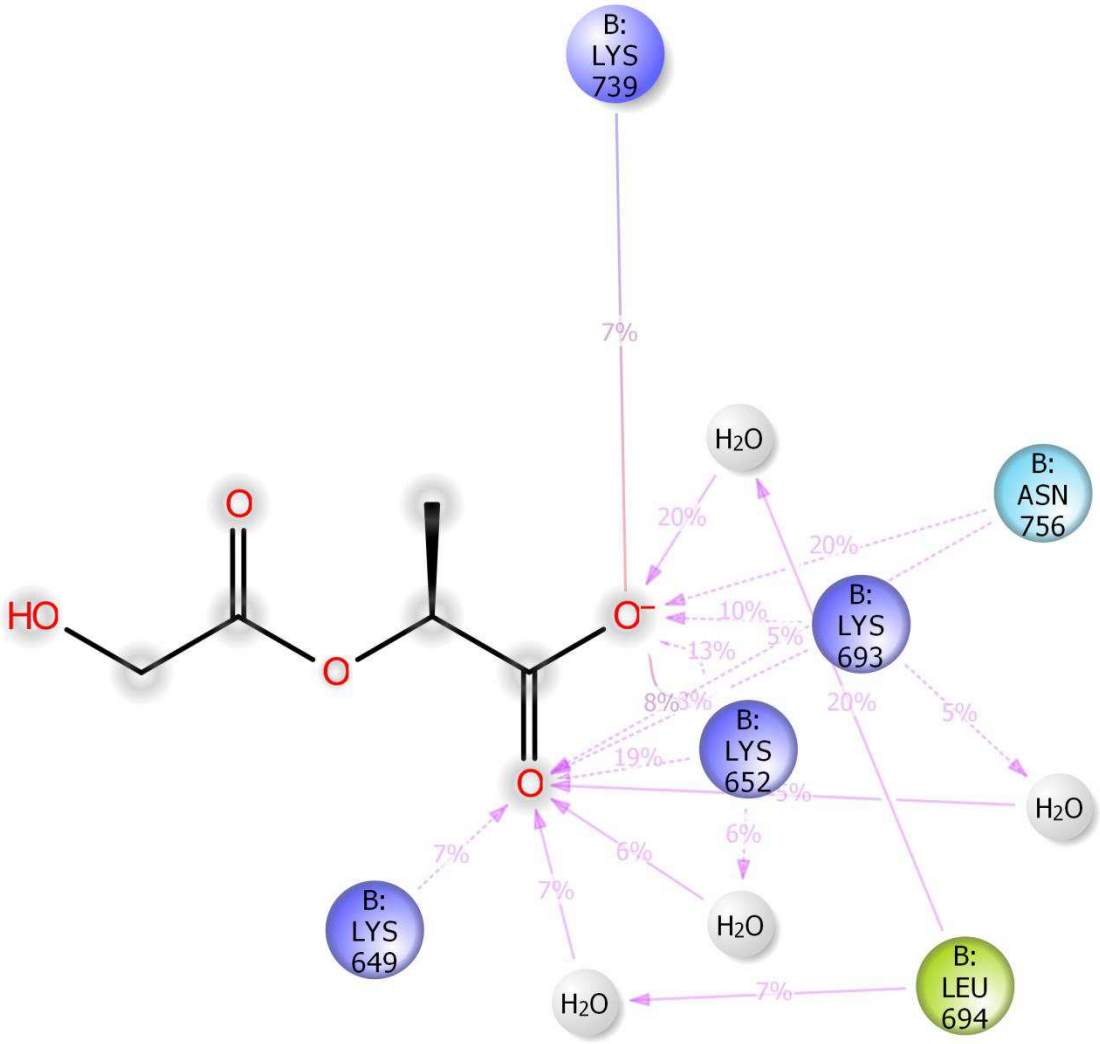


Figure 4C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