Computational Simulations for Preventing Crystallin Aggregation in Space Flights

ADITHYA RAJ[1,2] **AND GAURAV SHARMA**[2]

[1]*The Wardlaw-Hartridge School, NJ, Edison*
[2]*Eigen Sciences, NC, Apex*

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Cataracts are typically eye conditions in which there is clouding in the eye lens due to the clustering of crystallin protein. While cataracts typically develop slowly with age, astronauts are at increased risk due to accelerated protein aggregation from space radiation exposure. They may experience an accelerated onset of cataracts due to excessive exposure to space radiation. For future space exploration missions to be successful and for astronauts' health, it is essential to understand and address cataract risk factors. Preventing the clumping of these proteins could be an effective way to prevent crystal formation and address the risk of cataracts. Therefore, it can be hypothesised that the crystallin protein consists of a particular binding site that promotes their attachment and crystal formation. The research uses computational simulations to recognize chemical compounds that prevent crystal formation by binding the crystallin protein. As predicted by Prankweb machine learning, molecular docking simulations show that only carnosine, sorbinil, and zopolrestat successfully bind to the druggable site. Crystallin–ligand interactions were analyzed using the PLIP web server. Lastly, the pharmaceutical properties of these ligands were elucidated from the SwissADME, which reveals that all three selected ligands exhibit low blood-brain barrier penetration as well as high gastrointestinal absorption. The current exploration will offer a possible solution to diminish the risk of cataracts in future space missions.

1. INTRODUCTION

In recent years, astronauts returning from space missions have exhibited the development of a thin film over the lens of the eye—commonly diagnosed as cataracts [1, 2]. Before we understand why this happens, we need to know what a Cataract is. Cataract can be characterized by clouding of the lens of an eye, which is typically straightforward [1]. Cataracts are primarily caused by the aggregation of crystallin proteins in the aqueous environment of the eye lens.Crystallin proteins, essential components of the eye lens, gradually clump together as we age [1, 3], and ongoing research continues in search of a cure for cataracts [1]. Crystallin are highly stable, water-soluble structural proteins that make up the bulk of the vertebrate eye lens, maintaining its transparency and refractive index. In cataract, there are structural changes in these proteins that can lead to aggregation, producing insoluble light-scattering deposits that cloud the lens. Molecular docking is a computational drug discovery technique that predicts how a small molecule interacts with a target protein at the atomic level. These proteins are divided into three main types: alpha, beta, and gamma crystallins [3]. Alpha crystallins significantly help by preventing the aggregation of other lens proteins [4]. Beta crystallins are one of the major structural proteins in the eye lens, contributing to its transparency and refractive properties [5]. Gamma crystallins are mainly structural proteins that also contribute to cataract formation [6]. Any imbalance in any of these three crystallin proteins will cause cataract formation [3]. Cataracts are primarily caused by changes and damage to the crystallin proteins in the eye's lens, leading to clouding and loss of transparency [3]. Various types of crystallin proteins can be involved in the formation of cataracts. Here are some key points related to cataracts and crystallins.

Alpha crystallins (Alpha-A and Alpha-B) have chaperone-like functions, preventing the aggregation of other lens proteins [4]. Mutations or modifications in alpha crystallins can lead to a loss of their protective function, resulting in protein aggregation and cataract formation. Beta crystallins are essential structural proteins [5]. Any instability or mutation in these proteins can contribute to cataract formation due to lens proteins' disrupted structure and aggregation. Gamma crystallins are also structural proteins [6]. Mutations in gamma crystallins are mainly known to be associated with various congenital cataracts [7]. Aggregation of gamma crystallins can lead to opacities forming in the lens [6]. In summary, changes or damage to alpha, beta, and gamma crystallins can all contribute to the

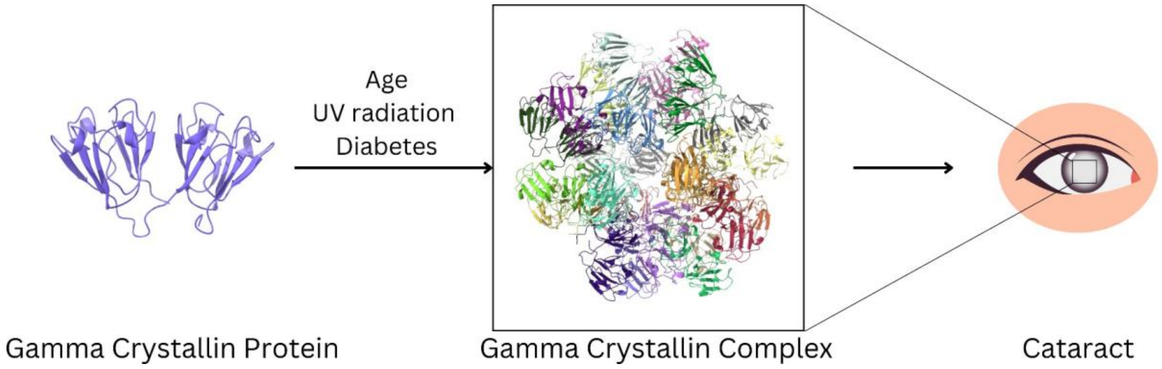

Fig. 1. Formation of cataract from the aggregation of the crystallin protein. Crystallin proteins are present in the eye and are essential for maintaining eye transparency. However, due to certain factors like age, UV radiation, and diabetes, the proteins get aggregated, resulting in insoluble crystals formation, which eventually leads to cataracts.

development of cataracts. Genetic mutations, post-translational modifications, and environmental factors such as UV exposure can all alter these proteins and lead to cataract formation.

Molecular docking is a computational technique used to predict the preferred orientation of a small molecule (ligand) when bound to a target protein, enabling the estimation of binding affinity and stability of the complex. [8]. In the discovery and development of the drug, this method plays a significant role as it permits the researchers to model the intended interaction between a drug candidate and its target protein, predicting the binding affinity and activity of the compound [8]. By simulating the docking process, scientists can identify potential drug candidates, optimize their structures, and understand the molecular mechanisms underlying the interactions [8]. Molecular docking accelerates the drug discovery process, reduces costs, and improves the efficiency of developing new therapeutics [8].

Elevated radiation exposure during spaceflight has been associated with early-onset cataract formation in astronauts [2]. We hypothesize that crystallin proteins contain specific binding sites that mediate aggregation, which supports their attachment and the formation of crystals. Blocking this binding site could restrict the crystallin interaction, thus preventing the opacity caused by the insoluble crystals. In this research, we conducted computational simulations to discover chemical compounds that can block the binding site. The crystallin protein has a negatively charged druggable site that aids crystal formation. Our docking simulations identified sorbinil and zopolrestat as possible inhibitors and will contribute to cataract prevention.

2. RESULTS

In this paper, we tried to offer a potential solution to reduce cataract risk during future space missions. In our current work, we have used the Prankweb server to get the crystallin druggable site. Prankweb is basically a machine learning-based method which is designed to predict the ligand binding sites on protein structures. It is a region where the clumping of 2 proteins occurs. Figure 2A illustrates the binding site present on the given crystallin protein. In the next step, we computed the ESP of the protein surface. The ESP map visualizes positive regions in blue, negative in red, and neutral in white areas of a protein. We used ChimeraX software to get the protein's ESP as illustrated in Figure 2B.

Molecular docking serves as a computational technique which shows how the interaction of ligand and protein occurs. Using the Hdock2.0 server we have obtained protein-ligand complex structures. Figure 3 displays the structures of the molecular docking simulations. We have used PLIP in order to understand the interactions between the ligands and the crystallin protein amino acids; based on PLIP software, at a distance of 1.82 and 3.23 Å, respectively, alrestatin formed two hydrogen bonds with THR and SER. Carnosine, at a distance of 3.14, 2.53, and 2.98 Å, formed three hydrogen bonds with GLU, ASP, and ASN respectively. Where Lanosterol formed no hydrogen bonds, Sorbinil formed four with 2 ASP and 2 ASN at 2.06, 2.14, 2.81, and 2.6 Å. Zenarestat formed three hydrogen bonds with ALA, TRP, and ASA at a distance of 2.76, 3.25, and 3.7 Å. Finally, zopolrestat has one hydrogen bond with Glu at a distance of 2.34 Å. Distance of hydrogen bonds ranges between 1.82-3.70 Å. ADME stands for absorption, digestion, metabolism, and excretion. We have used

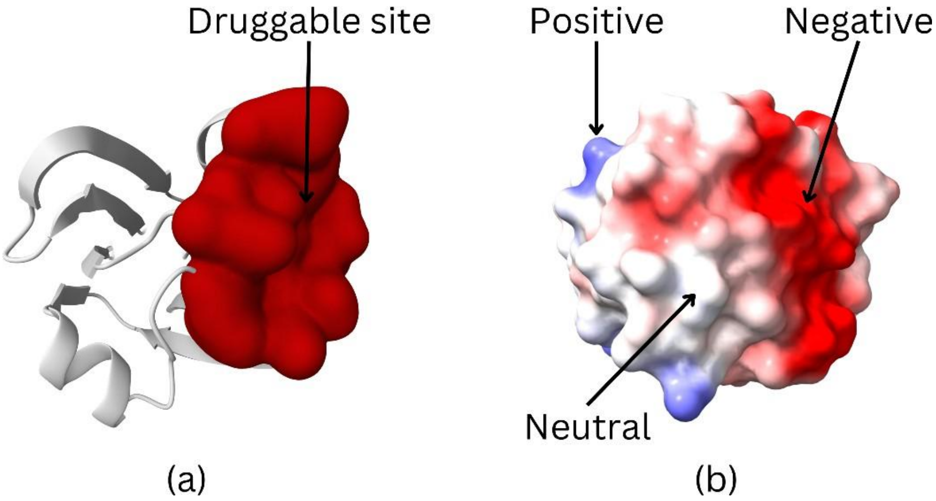

Fig. 2. Crystallin protein properties. (a) The druggable site predicted by machine learning is shown in red, and (b) the crystallin protein's electrostatic surface potential (ESP) is shown and calculated using the ChimeraX software. Red is negative, blue is positive, and white is neutral.

the SwissADME software to get the ADME properties of the ligands. With the exception of lanosterol, all six ligands exhibited substantial gastrointestinal (GI) absorption. The process by which medications or nutrients move from the gastrointestinal system into the bloodstream is known as high GI absorption. Every ligand has demonstrated drug-likeness and abides by the Lipinski's rule of five. Based on its molecular characteristics, a set of rules known as "drug-likeness" otherwise called as the Lipinski's Rule of Five, predicts the probability that a chemical compound will be an orally active drug in humans. None of the ligands, meanwhile, demonstrated BBB (blood-brain barrier) penetration. BBB permeability refers to the capability of a chemical to pass through the BBB, a barrier which prevents compounds from entering the brain from the bloodstream.

Finally, we computed the gamma protein complex formation using the AlphaFold 3 web server. The crystallin protein complex is shown in Figure 4. Gamma crystallin crystallization starts with structural instability brought on by environmental stressors such as UV rays, space radiation, or oxidative damage, which results in post-translational changes or protein misfolding. Because hydrophobic areas are exposed and protein-protein interactions are broken, gamma crystallin, primarily a structural protein, becomes more likely to aggregate. Insoluble protein clusters created by this aggregation cause cataract development and lens opacity. By blocking the binding sites implicated in these interactions, it may be possible to stop gamma crystallin crystallization and reduce the risk of cataracts. This computational insight highlights a viable structure-guided strategy for designing aggregation-inhibiting molecules to protect lens transparency during long-duration spaceflight.

3. DISCUSSION

The study specifically used γD-crystallin (PDB ID: 1HA4) as the protein target. This choice was based on γ-crystallin's well-documented role in cataract formation, particularly under conditions of structural destabilization from environmental stressors such as space radiation, UV exposure, or oxidative damage. While the exact aggregation mechanism differs across α, β, and γ subtypes, the docking and binding site prediction in this work focused solely on γD-crystallin. The predicted aggregation-promoting region corresponds to the primary druggable pocket identified by PrankWeb—located within the Greek key motifs of γD-crystallin, which span residues roughly 40–80 and 120–160. These domains are known from prior literature to contribute to hydrophobic interactions and protein–protein association in aggregation-prone states.

Pharmaceutical properties of the ligands. Gastrointestinal absorption is how drugs or nutrients pass through the gastrointestinal tract to enter the bloodstream. Blood-brain barrier Permeation is the ability of a substance to cross the blood-brain barrier. This protective layer restricts the passage of substances from the bloodstream into the brain. Drug likeness (Lipinski's Rule of Five) is a set of guidelines used to predict the likelihood that a chemical compound will be an orally active drug in humans based on its molecular properties. These properties were computed using the SwissADME webserver.

For people with young cataracts, medical management will consist of stronger glasses. Through surgery, the cloudy lens is removed from the eye and replaced with an artificial intraocular lens (IOL). Eye drops are used for healing, and recovery typically happens within a few weeks, with most people returning

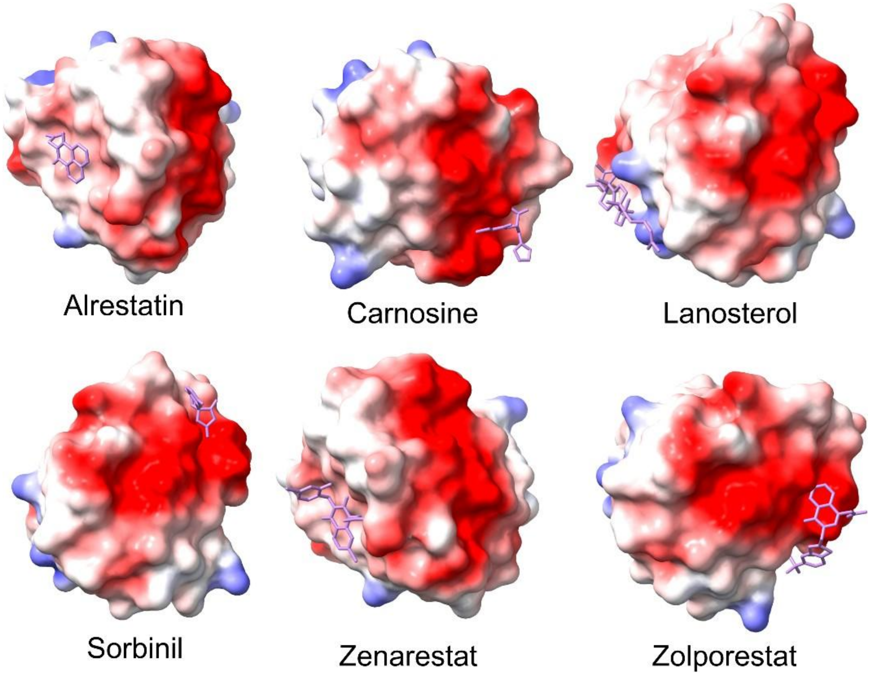

Fig. 3. Molecular docked structures of crystallin-ligand complexes. Only carnosine, sorbinil, and zopolrestat of the six ligands bind to the protein's binding site; hence, these ligands are more likely to prevent crystallin aggregation.

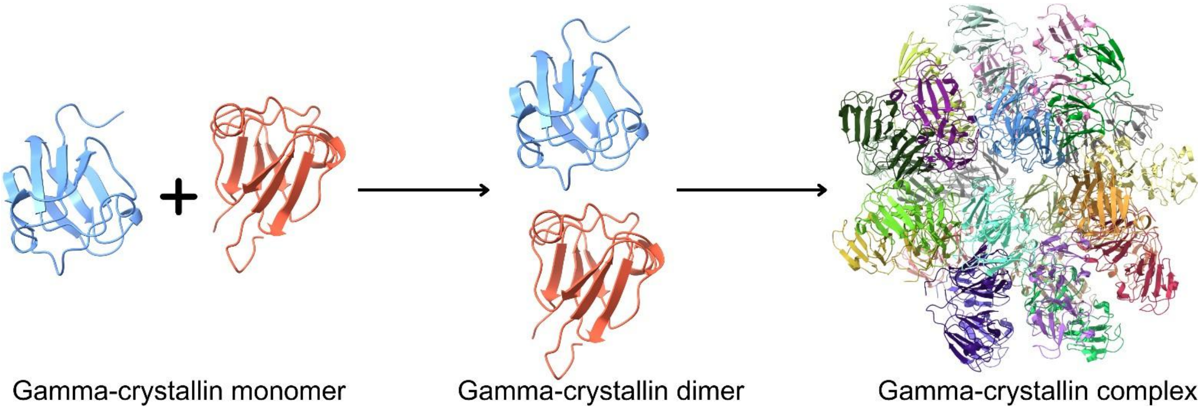

Fig. 4. Mechanism of crystalline formation. The figure explains how crystallin protein interactions were modeled using AlphaFold 3. In the first step, the crystallin protein interacts with the protein's binding site and eventually forms a gamma-crystallin complex, as shown in the right of the figure. A closer evaluation of the protein indicates that the significant interactions were at the druggable site of the protein.

to normal activities within a few days. We will conduct lab experiments to test and validate our findings in future studies. This will help us analyze our data under controlled conditions. We will increase the number of ligands used in the screening process. This may give us new patterns/trends within the ligands. Moreover, the exact mechanism should be studied by conducting experiments in space. This can provide results that cannot be done with Earth's gravitational pull.

One limitation of the research is that we only explored the gamma crystallin protein and its inhibition mechanism. In future research, we will explore the other two forms of crystallin protein, alpha and beta. We assume the current study will help us understand the different forms of crystalline complex formation. We will expand virtual screening to a broader chemical library (>1,000 ligands) using AI-guided clustering to identify novel scaffolds. In this research, we carried out various computational simulations in search of a solution to diminish cataract risk for astronauts. We want to prevent crystallization because once crystallin is crystallized, it is insoluble. If the ligands bind to the crystallin, it will block its binding site, stopping the development of cataract. According to our docking simulations, we found that sorbinil, carnosine, and zopolrestat could be an excellent binder to the crystallin protein. We also conducted interaction analysis using the PLIP web server, which provided us with the bonds generated between the ligands and the crystallin. As per the prediction of the binding site and number of interactions, we have found that sorbinil could be the most appropriate ligand that can prevent crystallin inhibition. The future application of this research is to pave the way in developing drugs against cataracts for astronauts traveling in space.

4. METHOD

The γD-crystallin 3D structure was downloaded from the PDB ID=1HA4 [9]. From the PubChem web server, six ligands were downloaded. Next, we used a website called P2Rank [Prankweb] in order to speculate the protein's druggable site [10]. Electrostatic surface potential was calculated and visualized using ChimeraX to assess the polarity and accessibility of the predicted binding site. [11]. Using Hdock molecular docking simulations were performed to obtain the complexes of the crystallin-ligand [12]. Protein–ligand interaction profiling was conducted using the PLIP web server, which automatically detects hydrogen bonds, salt bridges, hydrophobic contacts, π-stacking, and water bridges. SwissADME determined gastrointestinal absorption, blood-brain barriers, and drug likeliness [13]. Gastrointestinal absorption [GI absorption]: The drug is absorbed in your digestive system. alrestatin, carnosine, lanosterol, zenarestat, and zopolrestat all have high GI absorption. Sorbinil has low GI absorption. Blood Brain Barrier [BBB]: This stops the entry of all drugs from the blood. All six ligands have no BBB. Drug likeliness: This says whether a protein qualifies as a drug. All six ligands have a ‘‘yes ‘‘as their Drug likeliness. Finally, we used Google Alphafold 3 for the different crystallin complex structures. [9]. Six ligands were downloaded from the PubChem web server. Next, we used a website called P2Rank [Prankweb] to predict the druggable site of the protein [10]. After that, we received the electrostatic surface potential to get the Crystallin's charge using ChimeraX software [11].

5. CONCLUSION

In this study, we used a comprehensive computational approach to explore strategies for preventing crystallin protein aggregation, a key contributor to cataract formation in astronauts exposed to space radiation. Machine-learning–based binding-site prediction, molecular docking, electrostatic surface analysis, and interaction profiling collectively identified sorbinil, carnosine, and zolporestat as promising ligands capable of binding to a negatively charged druggable site on gamma-crystallin. Interaction analysis revealed stable hydrogen-bond networks, with sorbinil showing the strongest and most consistent interactions, suggesting its potential as an effective aggregation inhibitor. SwissADME analysis further supported the drug-likeness and favorable pharmacokinetic properties of these compounds. Together, these findings provide a mechanistic framework for inhibiting crystallin crystallization and highlight a computationally driven pathway toward developing preventive therapeutics for cataracts during long-duration space missions.

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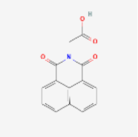
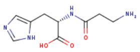
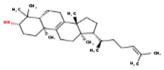
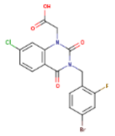
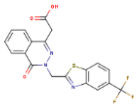
	alrestatin	**carnosine**	**lanosterol**	**sorbinil**	**zenarestat**	**zopolrestat**
Gastrointestinal Absorption	High	High	Low	High	High	High
Blood-brain barrier permeation	No	No	No	No	No	No
Drug likeliness (Lipinski)	Yes	Yes	Yes	Yes	Yes	Yes
2D structure						

Table 1: Pharmaceutical properties of the ligands. Gastrointestinal absorption is how drugs or nutrients pass through the gastrointestinal tract to enter the bloodstream. Blood-brain barrier Permeation is the ability of a substance to cross the blood-brain barrier. This protective layer restricts the passage of substances from the bloodstream into the brain. Drug likeness (Lipinski's Rule of Five) is a set of guidelines used to predict the likelihood that a chemical compound will be an orally active drug in humans based on its molecular properties. These properties were computed using the SwissADME webserver.

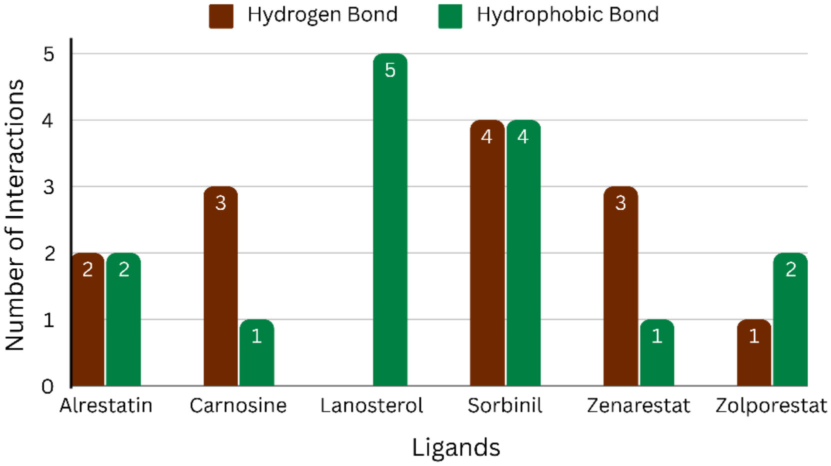


Figure 5: The number of interactions formed between Crystallin and ligands. These interactions were computed using the PLIP web server.