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Molecular docking and simulation studies of Chloroquine, Rimantadine and CAP-1 as potential repurposed antivirals for decapod iridescent virus 1 (DIV1)

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ABSTRACT

Drug repurposing is a methodology of identifying new therapeutic use for existing drugs. It is a highly efficient, time and cost-saving strategy that offers an alternative approach to the traditional drug discovery process. Past in-silico studies involving molecular docking have been successful in identifying potential repurposed drugs for the various treatment of diseases including aquaculture diseases. The emerging shrimp hemocyte iridescent virus (SHIV) or Decapod iridescent virus 1 (DIV1) is a viral pathogen that causes severe disease and high mortality (80 %) in farmed shrimps caused serious economic losses and presents a new threat to the shrimp farming industry. Therefore, effective antiviral drugs are critically needed to control DIV1 infections. The aim of this study is to investigate the interaction of potential existing antiviral drugs, Chloroquine, Rimantadine, and CAP-1 with DIV1 major capsid protein (MCP) with the intention of exploring the potential of drug repurposing. The interaction of the DIV1 MCP and three antivirals were characterised and analysed using molecular docking and molecular dynamics simulation. The results showed that CAP-1 is a more promising candidate against DIV1 with the lowest binding energy of -8.46 kcal/mol and is more stable compared to others. We speculate that CAP-1 binding may induce the conformational changes in the DIV1 MCP structure by phosphorylating multiple residues (His123, Tyr162, and Thr395) and ultimately block the viral assembly and maturation of DIV1 MCP. To the best of our knowledge, this is the first report regarding the structural characterisation of DIV1 MCP docked with repurposing drugs.

1. Introduction

Shrimp aquaculture is the practice of commercial rearing and harvesting of shrimp species in man-made environments. Its development has decreased the pressure caused by overfishing in marine ecosystems and raised the commercial supply of marine-based food, necessitating the development of a sustainable and eco-friendly industry. Aquaculture practices create artificial environments that allow exposure to biotic (pathogens) and abiotic conditions (pH) not encountered in their natural habitat [1]. Poor water quality and dense population may allow the transmission of pathogens, especially when crossing species barriers. Shrimp aquaculture, found in 60 countries accounts for just over half the world's shrimp supply with over 80 % of production is based in Asia. Demand for shrimp is expected to stay robust and interest in increasing this value chain include the development of disease control technologies for emerging diseases [2].

The shrimp hemocyte iridescent virus (SHIV), also known as Decapod iridescent virus 1 (DIV1), is an iridescent virus with a double-stranded DNA genome, classified within the proposed genus *Decapodiridovirus* within the family *Iridoviridae*. First reported in 2014, pond reared *Litopenaeus vannamei* shrimp in Zhejiang Province, China experienced massive die-offs while exhibiting hepatopancreatic atrophy with fading colour, empty stomach and guts, and softshell [3]. Histological sections revealed viral aetiology but with pathogenic symptoms that did

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Table 1
DIV1 MCP's top three proposed templates by different servers.

Protein enzyme	Server name	Template	Organism	Family	Length	Identity	E-value
Major Capsid Protein (ATE87157.1)	PSI-Blast	6OJN	Singapore grouper iridovirus	Capsid_NCLDV	537	38 %	3e-107
		5TIP	*Paramecium bursaria* Chlorella virus 1	Capsid_NCLDV	436	23 %	4e-19
	Phyre 2	6OJN	Singapore grouper iridovirus	Capsid_NCLDV	537	38 %	0
		5TIP	*Paramecium bursaria* Chlorella virus 1	Capsid_NCLDV	436	22 %	0
	Swiss Model	6OJN	Singapore grouper iridovirus	Capsid_NCLDV	537	39 %	N/A
		5TIP	*Paramecium bursaria* Chlorella virus 1	Capsid_NCLDV	436	21 %	N/A

Table 2
Summary of model validation using different tools.

Model evaluation tools	Normal range of the score	Obtained score	ATE87157.1
PROCHECK	>90 %	Before refinement	99.70 %
		After refinement	99.70 %
ERRAT	>50 %	Before refinement	67.43 %
		After refinement	73.56 %

not match the histopathologic characteristics of any known viruses. Genome sequencing has revealed that SHIV and *Cherax quadricarinatus* iridovirus (CQIV), identified from freshwater red claw crayfish *Cherax quadricarinatus*, are likely to be different strains of the same virus species [4]. In March 2019, the Executive Committee of the International Committee on Taxonomy of Viruses (ICTV) approved a proposal for a new species of Decapod Iridescent Virus 1 (DIV1) in the new genus *Decapodiridovirus*, to include SHIV and CQIV [5]. Species that are known to be susceptible is the Pacific white shrimp *Penaeus* (*Litopenaeus*) *vannamei* with detection in many susceptible penaeid species such as the Giant freshwater prawn *Macrobrachium rosenbergii* [6], Louisiana swamp crayfish *Procambarus clarkii* [3], Oriental freshwater shrimp *Macrobrachium nipponense*, Oriental prawn *Exopalaemon carinicauda* [6] and Redclaw crayfish *Cherax quadricarinatus* [7] indicating that DIV1 poses a new threat to the shrimp farming industry.

To date, the search for preventive treatment for SHIV/DIV1 is still ongoing. Current measures being utilised are conventional biosecurity practices such as surveillance and movement restrictions for farms, quarantine and removal of moribund or dead individuals from affected farms and testing for DIV1 in brood stock and post larvae. Treatment of aquaculture diseases has been reliant on the implementation of best practices and chemical treatment (chlorine). Novel experimental treatments or prevention of shrimp disease have been reported using probiotics [8,9], sulfate polysaccharides in the algal crude extracts [10], bioactive secondary metabolites [11], silver nanoparticles (AgNPs) [12] and immunostimulants [13]. Molecular biology efforts that have been attempted include the use of double-stranded RNA (dsRNA) to induce the host RNA interference (RNAi) antiviral mechanism and the use of endogenous viral elements (EVE) to provide shrimp with heritable tolerance to viral infections [14]. In addition, the development of vaccines for shrimp disease is ineffective as shrimp lack the adaptive immune system and rely on the inherent immune system to fight pathogens. Currently, there is no reported effort to explore the use of antiviral drugs in the treatment of viral diseases in shrimp aquaculture.

Focusing the Major Capsid Protein (MCP) as the target protein for this study on drug repurposing for DIV1 is a well-founded decision. MCP is a crucial component of the viral capsid, which is the protective outer shell of the virus [15,16]. It is responsible for forming the structural framework of the viral particle in several viruses, including DIV1 [17–19]. By targeting structural proteins like MCP, it is possible to disrupt multiple stages of the viral lifecycle. In the case of DIV1, interfering with MCP can impair viral assembly, maturation, and, ultimately, the virus's ability to infect host cells. Furthermore, MCP is often a conserved protein within a viral species, making it a constant and reliable target for drug development [17,20]. This consistency minimizes the probability of resistance forming quickly, which is a concern in the development of antiviral drugs. This fact is supported by the availability of structural information about MCP and allows researchers to predict how potential drugs might interact with the protein, which is a key step in drug repurposing research. Moreover, if this study successfully recognizes existing drugs that interact with MCP and inhibit DIV1, it could mitigate economic losses in shrimp farming by controlling DIV1 using MCP-targeted drugs.

Well-known examples of drug repurposing are Sildenafil that was developed for hypertension treatment but commercialized for the treatment of erectile dysfunction, dimethyl fumarate that has been repurposed from the treatment of psoriasis to multiple sclerosis and the sedative thalidomide being repurposed for the treatment of multiple myeloma and leprosy. However, these successfully reported drug repositioning is often a product of serendipity [21]. To further increase the success of drug repurposing to overcome the financial and time constraints faced during the traditional drug discovery process, researchers have relied more on the utilisation of bioinformatics and computational tools. The establishment of the Drug Repurposing Hub database (https://clue.io/repurposing) has boosted the computational screening of drugs by providing an annotated collection of FDA-approved drugs, clinical trial drugs, and pre-clinical tool compounds with a companion information resource [22].

Computational approaches that include molecular modelling [23], transcriptomic data mining [24] and molecular docking [25] have contributed to the screening of drugs for repurposing. As of date, computational screening has produced promising results such as the use of malaria drug amodiaquine as a potential anti-cancer agent [26] and ciprofloxacin for the treatment of Chagas disease that is caused by the parasite *Trypanosoma cruzi* [25], Ethambutol for African sleeping sickness [27] and Comtan for the treatment of tuberculosis [28]. The use of big-data, -omics technologies, machine learning algorithms and artificial intelligence will all offer unprecedented knowledge and tools to aid drug repurposing [29]. The present paper is the first structural characterization of DIV1 MCP. The 3D model of DIV1 MCP was generated and used for comparative modelling. Molecular docking and molecular dynamics simulation is used to identify and characterise the inhibition mode of three potential antivirals, Chloroquine, Rimantadine and CAP-1 against DIV1.

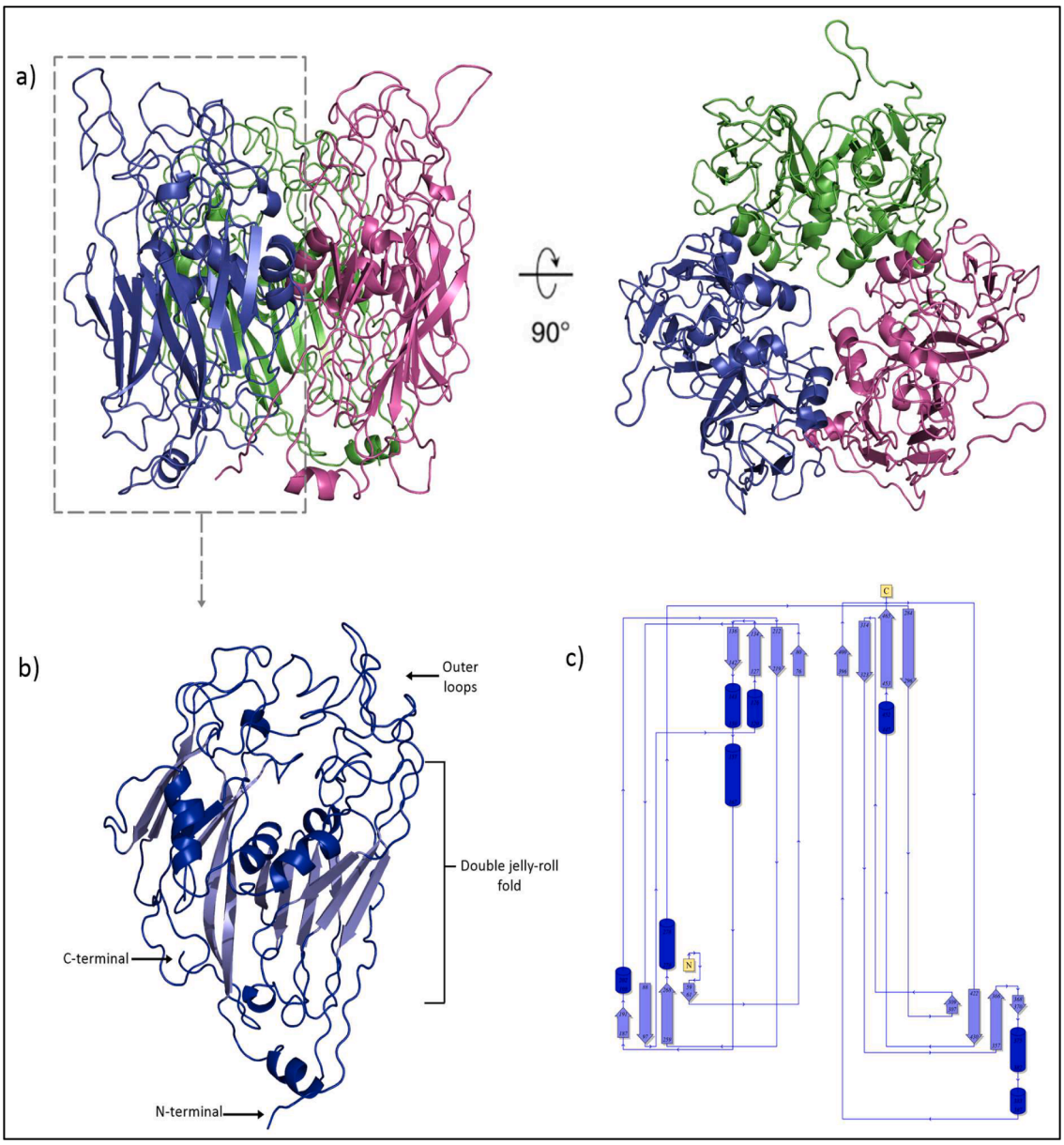


Fig. 1. Overall structure of DIV1 capsid protein. (a) Side view (left) and top view of DIV1 MCP trimer. (b) The secondary structure and (c) topology diagram of DIV1 MCP monomer. The β-strands are presented in light blue while α-helices in dark blue.

2. Methodology

2.1. Physiochemical characterization and sequence alignment

The target sequence was retrieved from the GenBank Database under accession no. ATE87157.1 and the full amino acid sequence was included in the supplementary file (Table S1). BLAST was employed to analyse the major capsid protein (MCP) derived from Decapod Iridescent Virus 1 (DIV1 MCP), which was isolated from the white leg shrimp, *Litopenaeus vannamei*. We conducted a BLAST search using the Protein Data Bank (PDB) as the database to identify a suitable crystal structure to serve as a template for our model. The physiochemical of DIV1 MCP were computed using the Expasy's ProtParam tool [30]. SUPER-FAMILY HMM server was utilised to identify the conserved domain and the potential protein family [31]. The multiple sequence alignment then was developed using Clustal Omega server [32] and ESPript 3 [33].

2.2. Model development and evaluation

The potential template of MCP was screened by using different servers that were PSI- BLAST [34], Phyre 2 [35] and Swiss Model [36]. The sequence of MCP has been optimized and the three-dimensional (3D) structure was built by using Swiss Model server. The 3D-model has been refined using 3D refine server [37] and evaluated by utilising PROCHECK [38] and ERRAT [39] server. The model was superimposed with the best template structure and their structural differences were determined. The chosen model of MCP was analysed its topology using PDBsum [40]. The quality scores of alignments between root mean square deviations (RMSD) were determined using TM-align program [41,42].

2.3. Molecular docking

The binding site was predicted using the binding site analysis tool in FTSite server [43] and Conserved Domain Database (CDD). The

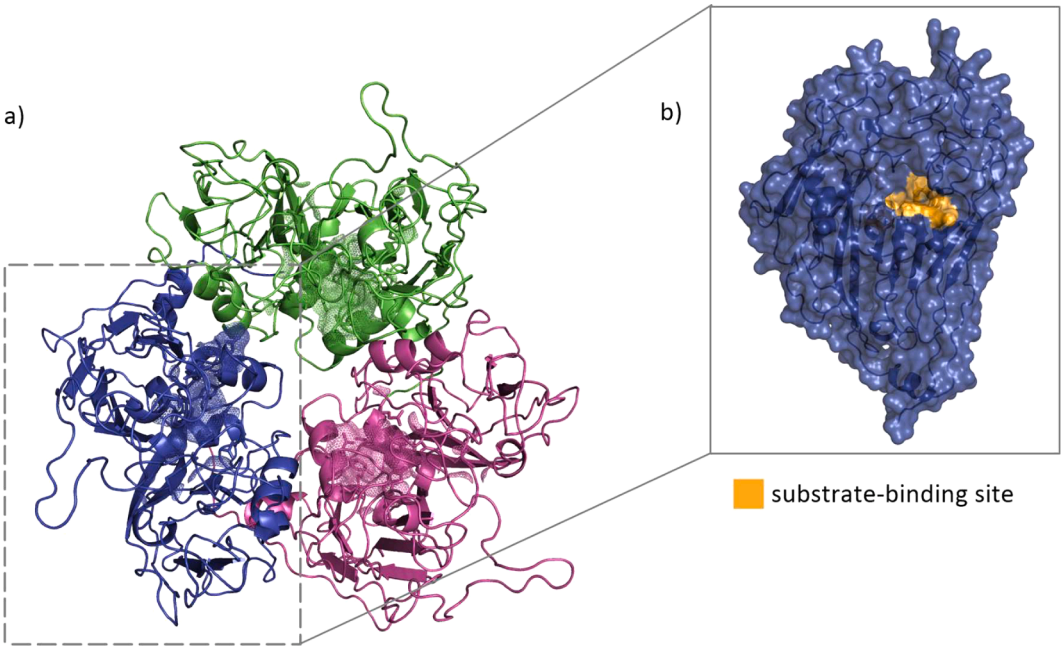


Fig. 2. The predicted binding pockets for DIV1 MCP. (a) The binding pocket of the MCP trimer. The predicted residues are represented in the mesh surface (blue, green and pink mesh surfaces. (b) A close up of the substrate-binding site is shown in orange surface representation. The binding sites were predicted using FTsite server.

structure of antiviral drugs, Chloroquine (PubChem CID: 2719), Rimantadine (PubChem CID: 5071) and CAP-1 (PubChem CID: 5,082, 818) were extracted from the PubChem server [44]. Molecular docking was performed by using SwissDock and the protein-ligand with the lowest binding energy was selected as a good binding affinity. Interactions of a protein-ligand complex was analysed using UCSF Chimera [45] and shown in schematic diagrams in 3D and 2D using BIOVIA Discovery Studio version 2020 [46].

2.4. Molecular dynamics simulation

To study the stability and molecular dynamics of DIV1 MCP interaction with the antiviral drugs, all proteins were simulated with different complexes (Apo, Chloroquine, Rimantadine and CAP-1). All protein-ligand docked complexes were subjected to MD simulation using GROMACS 2021 software package [47] and CHARMM36 force field [48]. The topologies and force filed parameters of all ligands were built separately using CGenFF server due to limitation of GROMACS program to parameterize the heteroatom groups and small molecules. The structures were placed at the centre of the cubic box which at least 10 Å from the edges and solvated with Simple Point Charge (SPC) water molecules. The system was neutralized by adding in accordance sodium ions to create zero charged system. Periodic boundary conditions (PBC) were applied to the proteins, and electrostatic interactions were improved by utilising the Particle Mesh Ewald (PME) summation technique, which is the best method for calculating long-range electrostatics. The energy minimization was performed using the steepest descent minimization of 5000 steps followed by equilibration for 100 ps of solute-position-restrained MD. LINCS algorithm (LINear Constraint Solver) was applied to constraint all bonds in the system. The MD simulations of the equilibrated structures were conducted in triplicate for a duration of 100 ns (100,000 ps). To assess the stability and compactness of the protein-ligand structure, GROMACS utilities; root mean square deviation (RMSD) of the backbone and radius of gyration (Rg) were calculated.

3. Results and discussion

3.1. Physicochemical characterization and sequence alignment

The physiochemical of MCP were computed using the Expasy's ProtParam tool. The result shows the molecular weight and theoretical pI of the target protein was 53,857.50 kDa and pI 7.59. The total number of negatively (Asp + Glu) and positively (Arg + Lys) charged residues was 50 –R and 51 + *R*. This target protein is classified as stable since the instability index was lower than 40. Decapod iridescent virus 1 (DIV1) is a large double-stranded DNA (dsDNA) virus in the family Iridoviridae. The protein sequence of DIV1 MCP was subjected to several proteins functional database PFAM, Conserved Domain Database (CDD) and SUPERFAMILY HMM server DIV1 MCP was classified as Major capsid protein belong to family nucleocytoplasmic large DNA viruses (Table S1). The sequence alignment of major capsid protein from DIV1 showed high homology to MCP from Singapore Grouper Iridovirus (PDB ID: 6OJN) and *Paramecium bursaria* Chlorella virus 1 (PDB ID: 5TIP) with 38 % and 23 % sequence identity respectively.

3.2. Model development and evaluation

The potential template that best resembles the target protein was identified using three different servers, PSI-Blast, Phyre 2, and Swiss Model. As a result, two templates 6OJN and 5TIP appeared with different percentages of identity obtained from different servers, and amongst both templates, 6OJN was chosen as the best template as it showed the highest sequence identity with the target protein (DIV1 MCP) compared to 5TIP (Table 1). Thus, the three-dimensional (3D) structure of DIV1 MCP was constructed based on the crystal structure of Singapore grouper iridovirus (PDB ID:6OJN) as a template using the Swiss Model server. The initial 3D structures of DIV1 MCP were further optimized by 3D refine server to exclude poor molecular contacts and refine the sidechains. Two structure evaluation tools, PROCHECK and ERRAT were implemented to validate the quality of the created 3D models before and after structure refinement (Table 2). The Psi/Phi Ramachandran plot from the PROCHECK analysis was used to examine the backbone conformations of the protein. According to the

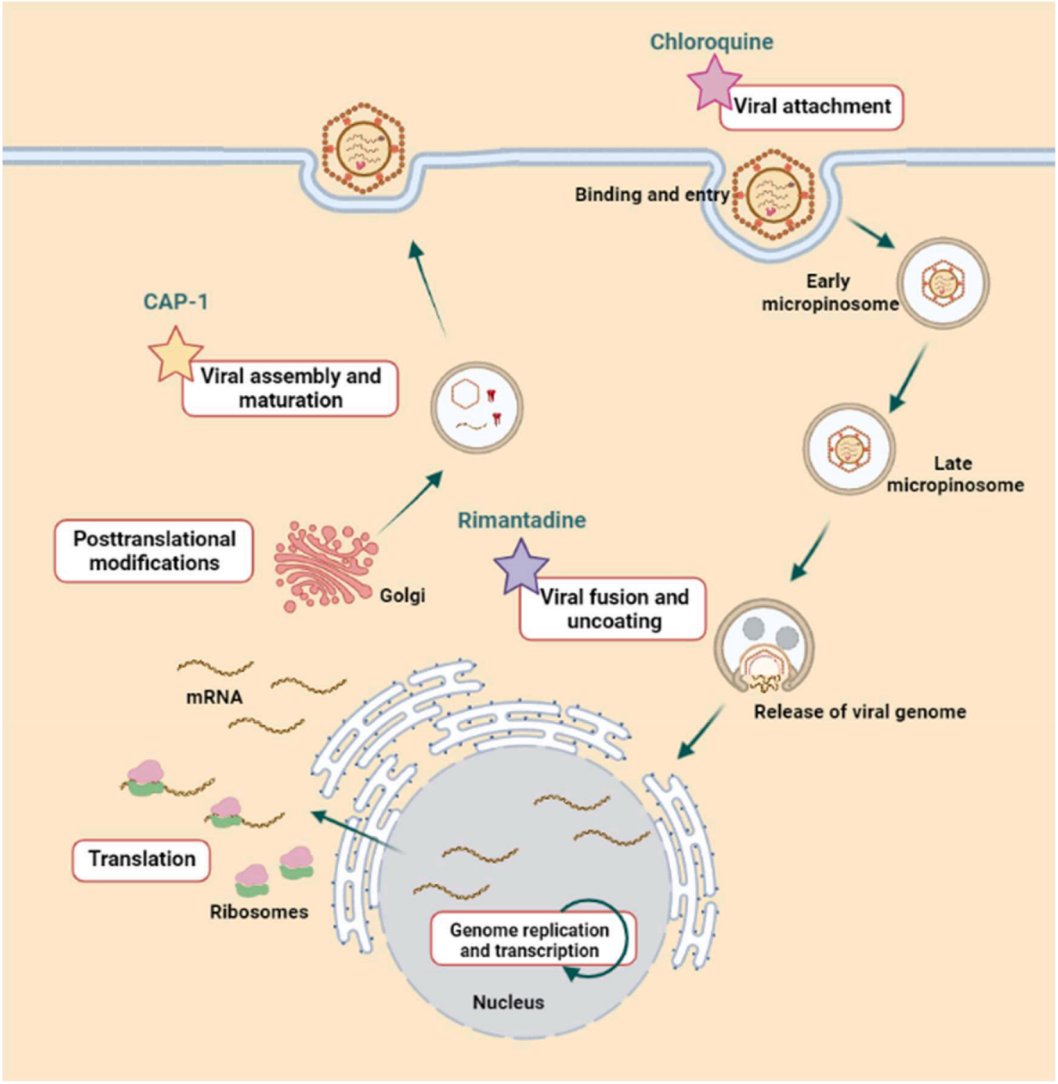


Fig. 3. Schematic illustration of antiviral drug mechanism against DIV1 virus replication. Modified from Refs. [60,61]. This illustration was created with BioRender.com.

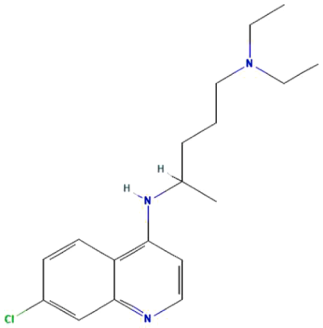
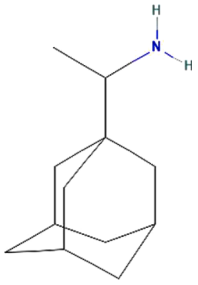
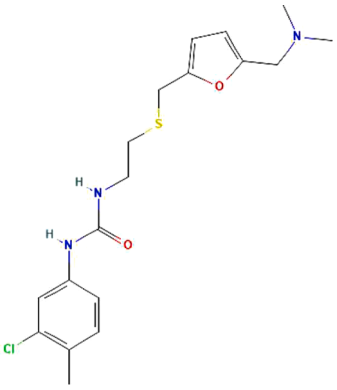
Ramachandran plot, 99.70 % of residues are in allowed regions and only 0.3 % of amino acid residue are in disallowed regions. A model with a score of more than 90 % is considered to be of good stereochemical quality [38]. To calculate the overall quality score for non-bonded atomic interaction, model validation was also performed by ERRAT. The ERRAT score of the MCP model was significantly improved with a score 73.56 %. Based on [49], the normal range of ERRAT score to be accepted for a high-quality model must be greater than 50 % therefore, indicate the DIV1 MCP model as a good quality model. The superimposition of the model (DIV1 MCP) with the template (6OJN) revealed a good structure alignment with RMSD of 0.38 Å and a 98 % coverage of the backbone atoms. The result of TM-score for the alignments showed 0.98 indicating that this structure alignment represents a better template as a score above 0.4 is regarded as significant. Subsequently, we also performed a comparative analysis with AlphaFold. The structural alignment assessment demonstrated that the model generated by Swiss Model exhibited a lower RMSD value and achieved a higher Tm-align score in relation to the template 6OJN, as compared to the model produced by AlphaFold. Based on this evaluation, we opted to employ the model produced by the Swiss Model server (Fig. S1). Despite their low sequence similarity, MCP and the other members of the nucleocytoplasmic large DNA virus family have a high degree of structural similarity. In addition, the secondary structure of the DIV1 MCP trimer displayed eight α-helices and a signature double jelly-roll fold with 16 ß-strands forming two antiparallel sheets as depicted in Fig. 1. This prevalence of double jelly-roll fold is known as a core structural motif that appears amongst capsid proteins and might be related to the viral shell formation of varying sizes [50,51].

3.3. Molecular docking

Before starting a molecular docking, the target protein was submitted to FTSite server to find the binding site region. Binding site identification is important for structure-based prediction of function and drug design. With near-experimental accuracy, FTSite is capable of predicting the binding sites in over 94 % of all proteins [43,52]. Fig. 2 depicts the position of the structural target protein binding site predictions in trimer: pink, green, and blue. The amino acids such as Asn120, His123, Asp147, Asn150, Gln151, Tyr162, Asn163, Ile166, Gly167, and Arg323 were predicted as binding sites for the substrate-binding site of DIV1 MCP protein.

Chloroquine, Rimantadine and CAP-1 were chosen as potential antiviral drug due to these compounds have several abilities to block viral capsid. Different compounds are categorized based on the viral cycle stage with which they interact, and their mechanisms were summarized in Fig. 3. Rimantadine is an M2 ion channel inhibitor and is

Table 3
The binding energy of the potential drugs with the DIV1 MCP.

Drug	PubChem CID	Structure	Binding energy (kcal/mol)
Chloroquine	2719		−7.25
Rimantadine	5071		−6.62
CAP-1	5,082,818		−8.46

used to suppress influenza A infection. It prevents viruses from replicating by interfering with the virus's uncoating process [53,54]. As for CAP-1, according to [55] and [56], CAP-1 is an antiviral drug used to inhibit HIV replication by preventing the assembly of viral capsids. Recent studies reported that Chloroquine used as an antiviral drug and potently fights the SARS-CoV-2 (Covid-19) pandemic by blocking the entry stage of viral replication even at low concentrations were used [57–59]. However, these compounds have been tested in humans, and to the best of our knowledge, there is no reported data regarding those compounds being used as antiviral drugs to treat viral infections in shrimp aquaculture. Thus, this is the first report on the structural characterisation of DIV1 MCP docked with repurposing drugs.

The finding revealed that three drugs i.e. Chloroquine, Rimantadine, and CAP-1 showed significant binding energies with DIV1 MCP protein as presented in Table 3. Amongst those compounds, CAP-1 has shown such a promising repurpose drug candidate against DIV1 as it possesses the lowest binding energy of −8.46 kcal/mol. Besides, the respective compounds have shown various interactions including van der Waals, hydrogen bonds, and alkyl while their active sites lie in a deep pocket shaped by α helical barrel loops as presented in Fig. 4.

Docking results showed that the active centre pocket of the DIV1 MCP-ligands (Chloroquine and Rimantadine) complexes consists of ten binding residues which are similar to the prediction result of the substrate-binding site obtained by FTsite server. Meanwhile, the DIV1-CAP-1 complex showed nine binding residues (Gly167 is excluded) recognised as active sites. As can be seen from Fig. 4, most residues of DIV1 MCP interacted with three compounds via van der Waals forces. These interactions occur between hydrophobic side chains which are essential to protein stability and function, especially for macromolecular complex structures such as DIV1 MCP trimer [62].

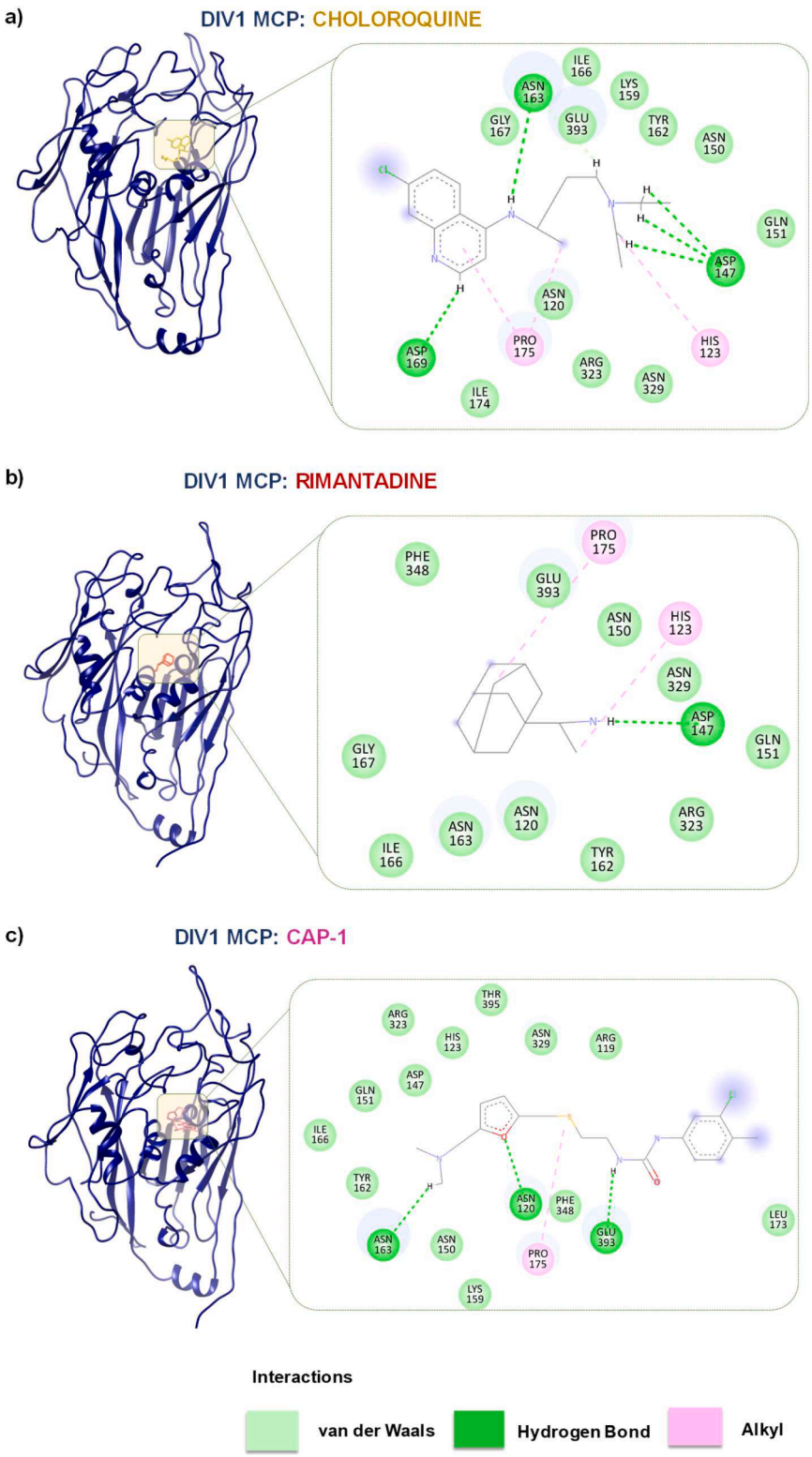


Fig. 4. The interactions of DIV1 MCP with (a) Chloroquine (b) Rimantadine and (c) CAP-1 compounds. The residues involved in the various interactions including van der Waals, hydrogen bond, and alkyl were indicated in light green, green, and lavender colours, respectively. Those interactions were created by using 2D schematic diagrams using Discovery Studio 4.0 (DS 4.0).

3.4. Molecular dynamics simulation

Molecular dynamics simulations were conducted in triplicate, with replicate 1 (R1), replicate 2 (R2), and replicate 3 (R3), each running for 100 ns. These simulations were performed to investigate the stability of DIV1 capsid protein complexes. The RMSD of the apo structure exhibited the highest deviations compared to the complex structure of the DIV1 capsid protein with antivirals, with RMSD values of 0.77 nm (R1), 0.71 nm (R2) and 0.73 nm (R3). The DIV1 MCP-CAP-1 complex demonstrated the most stability with RMSD values of 0.59 nm (R1),

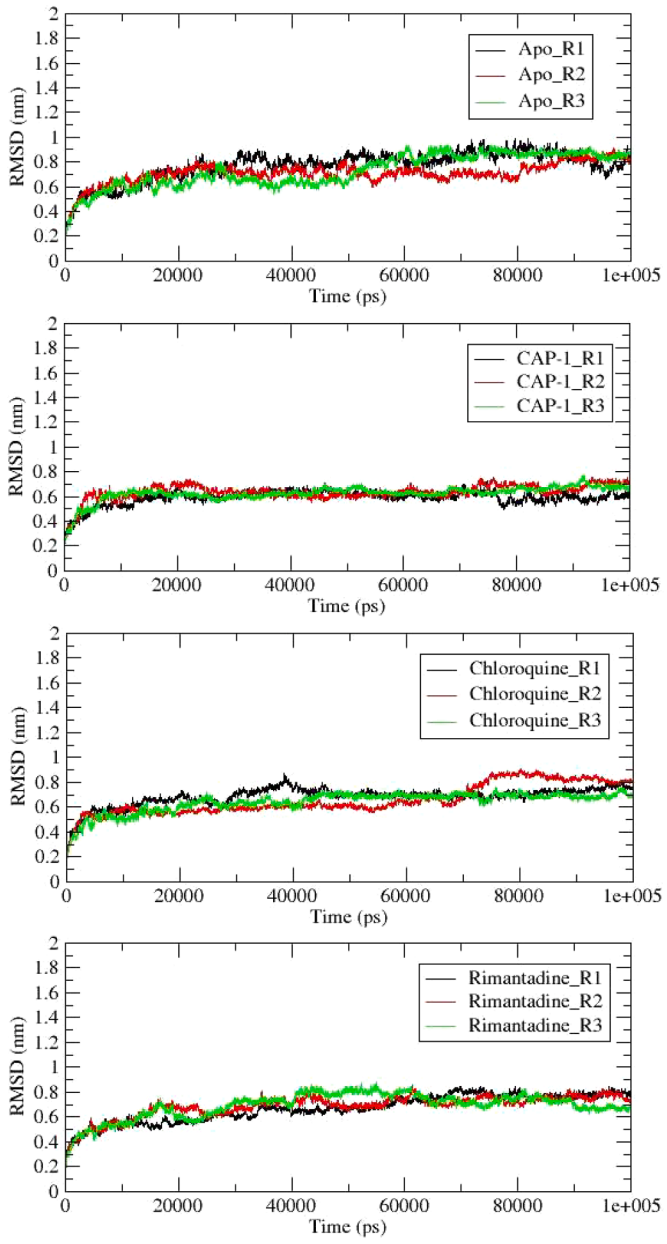


Fig. 5. Molecular dynamics analysis of apo and DIV1 capsid protein-ligand complexes (Chloroquine, Rimantadine, and CAP-1) trajectories generated by GROMACS. The MD simulations were conducted in triplicate (referred to as R1, R2, and R3) for a duration of 100 ns each.

0.63 nm (R2) and 0.62 nm (R3) compared to other complexes. The DIV1 MCP- Chloroquine and DIV1 MCP-Rimantadine exhibited slightly lower stability, as indicated by their RMSD values ranging from 0.66 nm to 0.69 nm (Fig. 5). These findings indicate that the sustained stability of the complexes are implied by the binding of the antivirals to DIV1 MCP. By taking together the result of docking and molecular dynamics simulation, therefore, it has been proved that the DIV1 MCP-CAP-1 complex is the most stable compared to other complexes.

The data of structural alignment evaluation of the DIV1 MCP model with its template, Singapore grouper Iridovirus (6OJN) showed 98 % of coverage, describing that their phylogenetic relationship of iridovirus was related. Decapod iridescent virus 1 (DIV1) is the only species of the new genus Decapod iridovirus and is included in the family Iridoviridae. It is an emerging viral pathogen that critically threatens shrimp aquaculture [6,63,64]. Thus, the mechanism of control and prevention for this disease remains scarce and elusive [60] reported that proteomic analysis of infected cells by iridovirid type revealed that the iridoviral replication involved phosphorylation reactions to increase the expression of that viral genome. Therefore, to stop this type of viral replication, a selective inhibitor or drug should be derived from a group that could block the assembly of viral at the late stage because the phosphorylation reaction is one of the post-translational modifications that occur at the final stage (Fig. 3) [65]. This fact can be related to the mechanism of antiviral drug, CAP-1 which functions to prevent the assembly of viral capsids and lead to the inhibition of viral replication [61].

Intriguingly, our findings demonstrated that CAP-1 showed the highest binding affinity (−8.46 kcal/mol) to DIV1 MCP protein, and compared to other drugs, CAP-1 had phosphorylated multiple residues such as His123, Tyr162, and Thr395. This fact has been corroborated by previous studies where CAP-1 had decreased the multimerization of viral and affected the stability and assembly of viral capsids which occur at the late stage [56]. Moreover, CAP-1 binding to viral protein induced the conformational changes that cause displace of residues Phe32, His62, and Tyr145 within the pocket of binding site and shifted the loop between two alpha helices of the viral protein structure. Consequently, it causes a loss of mature capsid assembly [56,66–68]. Therefore, we speculated that CAP-1, a repurposing drug could inhibit the viral assembly and maturation of DIV1 MCP by interfering phosphorylation of the viral protein.

Regardless, this study is primarily focused on the prediction of potential antiviral drugs targeting DIV1 replication and viral infectivity. While the results of molecular docking and molecular dynamics simulations have revealed intriguing interactions between the selected drugs and the DIV1 MCP, it's important to note that the scope of the study is limited to computational predictions. The aim here is to identify candidate drugs for further investigation, and as such, the study does not include experimental validation or verification of these predictions. Future research and experimental studies would be essential to confirm the effectiveness of the identified drugs in inhibiting DIV1 replication and controlling viral infectivity in practical settings, particularly within the context of shrimp farming.

4. Conclusion

In conclusion, the present study determined the physicochemical features, model development of the DIV1 MCP, and investigated the interactions of DIV1 MCP with three antiviral drugs i.e. Chloroquine, Rimantadine, and CAP-1. Amongst those drugs, CAP-1 has shown such a promising repurpose drug candidate against DIV1 as it possesses the lowest binding energy and good stability. We speculate that CAP-1 binding may induce the conformational changes in DIV1 MCP structure by phosphorylating multiple residues such as His123, Tyr162, and Thr395 and ultimately block the viral assembly and maturation of DIV1 MCP. This fact indicates that viral infectivity is critically dependant on capsid formation and stability, making the capsid protein a potentially attractive antiviral target. To the best of our knowledge, this is the first report regarding the structural characterisation of DIV1 MCP docked with repurposing drugs. In the future, *in vitro* and *in vivo* studies are required to corroborate the ability of CAP-1, a repurposing drug to treat the infection of Decapod Iridescent Virus 1 (DIV1) in shrimp farming.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgement

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.fsirep.2023.100120.

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