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Red Fruit Carotenoids as SARS-CoV-2 RdRp Inhibitors: An in Silico Study

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Abstract: Understanding the molecular interactions between natural bioactive compounds and viral proteins is essential for exploring the therapeutic potential of tropical plant resources. This study aimed to investigate the molecular interactions between carotenoids from Pandanus conoideus Lam. and the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) using an in silico molecular docking approach. The crystal structure of RdRp (PDB ID: 7D4F) was retrieved from the Protein Data Bank and prepared using YASARA-Structure. The docking protocol was validated through native ligand redocking, yielding a root mean square deviation (RMSD) of 1.8285 Å, confirming the reliability of the docking procedure. Eight carotenoid compounds were evaluated and compared with Remdesivir as the reference ligand. Although Capsanthin 3,6-epoxide exhibited the most favorable predicted binding energy (−6.755 kcal/mol), Cryptocapsin demonstrated the most biologically relevant interaction profile by forming hydrogen bonds with the catalytic residues Ser759 and Asp760, supported by hydrophobic and van der Waals interactions. The remaining carotenoids also interacted with the RdRp active site through distinct binding patterns. These findings provide molecular insights into carotenoid–RdRp interactions and highlight Pandanus conoideus as a valuable tropical source of bioactive compounds for early-stage antiviral research. Further molecular dynamics simulations, ADMET profiling, and experimental validation are required to confirm the biological significance of these computational predictions.

Keywords: Carotenoids; Molecular docking; SARS-CoV-2 RdRp; Tropical bioresources.

Introduction

In recent years, global attention has increasingly focused on the interconnection between environmental sustainability, biodiversity conservation, and human health (IPBES 2020; Keesing et al, 2010). The post-pandemic era has revealed that maintaining ecological balance and protecting local biodiversity are not only environmental priorities but also crucial strategies for strengthening community resilience against emerging diseases (Lawler *et al.,* 2021). Natural products derived from indigenous plants have gained renewed interest as potential bioactive agents that promote both ecological sustainability and public health (Thomford et al. 2018; Zeng et al. 2024).

Among the diverse natural resources found in Indonesia, the red fruit, Pandanus conoideus Lam., represents an exceptional example of an underutilized yet valuable bioresource (Heriyanto *et al*., 2021; Trisnawaty 2024). This species is native to Papua and has long been used by local communities for food, traditional medicine, and cultural rituals (Murtiningrum, 2012). The fruit is widely recognized for its vibrant red oil, rich in carotenoid pigments that exhibit antioxidant, anti-inflammatory, and potential antiviral properties (Heriyanto et al. 2021; Umar 2021; Ananto et al. 2024). Such characteristics position P. conoideus as a promising candidate for sustainable biotechnological applications and aligns with JBEE discussions on biodiversity conservation and the sustainable use of local natural resources (Hidayat et al., 2025; Cahyani et al.,

2025; Yantewo, 2024).

Carotenoids are natural isoprenoid pigments that are important for photosynthesis, safeguarding plants from light damage, and helping them adapt to environmental challenges like too much light, UV radiation, and oxidative stress. Producing and gathering these pigments helps to keep photosynthesis efficient and protects plant cells from harmful reactive oxygen species. In addition to their role in nature, carotenoids have known antioxidant qualities that help eliminate free radicals and lessen oxidative harm, which plays a part in preventing disorders related to oxidative stress in people. In recent years, increasing evidence has suggested that several natural carotenoids also exhibit antiviral potential through multiple mechanisms, including modulation of host immune responses and direct interactions with viral proteins identified through computational and experimental studies. These biological properties make carotenoids attractive candidates for molecular interaction studies and support their exploration as bioactive compounds using sustainable in silico approaches.

This computational strategy aligns with the global movement toward environmentally responsible research, often referred to as "green computational chemistry." By enabling the early-stage screening and prioritization of bioactive compounds, in silico approaches can reduce the number of compounds requiring synthesis and experimental testing, thereby improving research efficiency while minimizing resource consumption and laboratory waste (Annam, 2026). However, computational predictions are intended to complement rather than replace in vitro and in vivo studies, which remain essential for validating biological activity and safety. Consequently, in silico modeling serves as an efficient and sustainable preliminary tool for natural product research, supporting both scientific innovation and environmental stewardship in line with sustainable development goals.

Given the ecological and biomedical potential of Pandanus conoideus, exploring its carotenoid constituents through computational analysis is a timely and relevant approach. Understanding their interaction with viral and microbial targets can help identify natural molecules that may support human health while valorizing local biodiversity. Moreover, studying the physicochemical and ADMET properties of these compounds helps assess their biocompatibility and environmental safety, ensuring that their potential applications align with the principles of sustainable health and green technology.

Therefore, this study aims to investigate carotenoid compounds from red fruit (Pandanus conoideus Lam.) through an in silico approach to evaluate their potential as candidate inhibitors of SARS-CoV-2 RNA-dependent RNA polymerase (RdRp). This research is expected to provide scientific insight into the antiviral potential of local natural compounds and support the development of bioactive agents derived from Indonesian biodiversity for future therapeutic applications.

Materials and Method

The molecular docking analysis was conducted on a computer equipped with an Intel Core i3-7100U CPU at 2.40 GHz and 4 GB RAM running a Windows operating system. The primary software installed is YASARA-Structure 24.4.10 and Discovery Studio Visualizer (DSV) 21.1.0.20298.

The structural data for SARS-CoV-2 RdRp (PDB ID: 7D4F) were obtained from the Protein Data Bank through https://www.rcsb.org/ (Yin et al., 2021). This structure underwent preparation, including removing water molecules and ions using YASARA-structure tools. While the native ligand, (8-(3-(3-aminobenzamido)-4-methylbenzamido) naphthalene-1,3,5-trisulfonic acid), remained for benchmarking the potential of herbal bioactive compounds as competitors. To validate the docking methodology, redocking with 25 iterations of the native ligand was conducted utilizing the YASARA-structure. Preparation initiates with the separation of the protein from its native ligand. Subsequently, all alterations to compound configurations undergo energy minimization before advancing to the molecular docking phase.

The docking procedure used to calculate binding energy values was performed in YASARA-Structure using the Vina docking method and the AMBER force-field-based scoring approach. The docking cell was automatically generated by YASARA-structure based on the position of the co-crystallized native ligand. A simulation sphere with a radius of 5.0 Å surrounding the outermost atoms of the original ligand was used to achieve full coverage of the binding pocket while reducing unnecessary exploration outside the active site. The Vina

docking approach embedded in YASARA-structure was utilized for calculating binding energies, and the receptor residues involved in the interaction were pinpointed. After finishing the docking procedure, the outcomes were stored in the PDB (.pdb) file format. Then, the data obtained after docking was analyzed and visualized with DSV (Ananto et al, 2025; Ananto et al, 2026). Papuan Red Fruit, scientifically known as Pandanus conoideus Lam, is notable for its carotenoid content, as detailed in Table 1 (Heriyanto et al. 2021). The docking process was conducted for this fruit's carotenoid compounds.

Three-dimensional representations of carotenoid compounds were sourced from the PubChem database in SDF format. These structures were transformed into PDB format and underwent geometry optimization and energy minimization with the assistance of YASARA-Structure software before performing molecular docking. During ligand preparation, hydrogen atoms were added automatically, bond orders were assigned, and the structures were optimized using the AMBER force field to obtain energetically favorable conformations suitable for docking

Results and Discussion

The molecular docking process was conducted using the crystal structure of SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) (PDB ID: 7D4F), obtained from the Protein Data Bank (https://www.rcsb.org) (Yin et al. 2021). Prior to docking, the structure was prepared by removing all water molecules and ions using the YASARA-Structure software. The native ligand was retained as a reference to evaluate the binding potential and validity of the bioactive compounds under investigation.

The SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) with the PDB ID 7D4F is one of the most critical molecular targets for inhibiting viral replication. RdRp is an essential enzyme used by the virus to replicate its RNA genome, meaning that without its activity, the virus is unable to reproduce within host cells. Consequently, RdRp has become a primary target in the development of antiviral drugs for COVID-19 therapy.

YASARA-Structure software was employed in this study to perform various molecular structure analyses, includ ing the separation of ligands from the protein complex. In this work, YASARA-Structure was specifically utilized to isolate the native ligand from the target protein. Once the separation was successfully completed, the next step involved validating the molecular docking protocol. This validation step is crucial to ensure that the docking method applied is accurate and reliable. The verification was conducted by redocking the original ligand into the binding site of its receptor. The obtained root mean square deviation (RMSD) value was 1.8285 Å, indicating the average positional difference between the re-docked and the crystallographic poses of the ligand. A low RMSD value indicates that the re-docked ligand closely reproduces the experimentally determined binding orientation, demonstrating that the docking protocol used in this study possesses a high degree of accuracy and reliability (**Figure 1**).

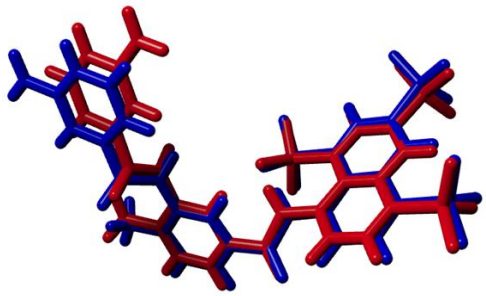


Figure 1. Validation of the molecular docking protocol. The blue structure represents the native ligand, while the red structure represents the ligand conformation obtained after the redocking process (RMSD = 1.8285 Å)

The molecular docking method was executed through a sequence of organized stages intended to clarify the interactions between carotenoid molecules derived from Pandanus conoideus (red fruit) and the target enzyme RNA-dependent RNA polymerase (RdRp). The first and most significant phase in the docking process was energy minimization, which aimed to achieve the most stable structure of each ligand before docking. All carotenoid compounds found in the red fruit underwent energy minimization using the steepest descent optimization method to guarantee that the system attained its lowest energy condition. For comparative purposes, remdesivir was added as a clinically significant antiviral reference.

The molecular docking simulations took place on the YASARA-Structure platform. The primary goal of this procedure was to find the best binding sites and orientations of the carotenoid compounds and reference drugs within the active site of the SARS-CoV-2 RdRp

enzyme. The docking process consisted of various essential steps, including establishing a simulation box based on the coordinates of the native ligand. The dimensions of the grid box were set by extending 5 Å in every direction (x, y, and z axes) from the outermost atoms of the native ligand.

Each docking pose was evaluated in terms of binding energy, hydrophobic and electrostatic interactions, and other relevant parameters. **Figure 2** shows how the ligands connect with their target receptors in the specified simulation box, offering a straightforward depiction of their placements and binding styles within the active site of SARS-CoV-2 RdRp. The molecular docking findings for all carotenoid substances found in Pandanus conoideus (the red fruit), along with the reference medications remdesivir and paxlovid, are detailed in Table 1. This table also presents the computed binding energies and the particular interactions established between each ligand and the amino acid residues of the SARS-CoV-2 RdRp enzyme. The important amino acid residues situated in the active-site cavity are emphasized in bold to highlight their vital function in ligand attachment and enzyme activity. The active site of SARS-CoV-2 RdRp serves as a crucial structural element that is necessary for facilitating the replication of the viral RNA.

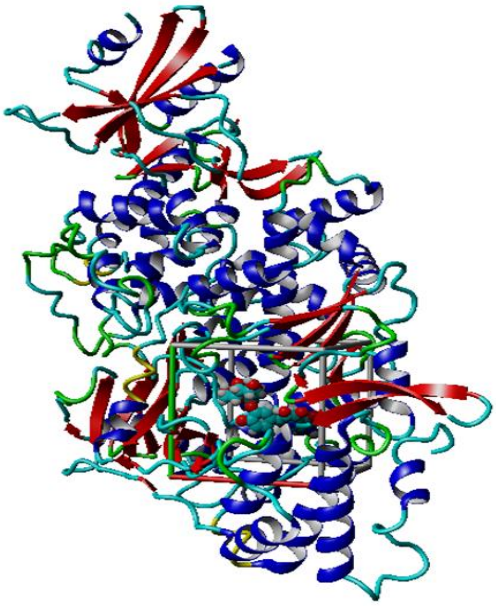


Figure 2. Visualization of the molecular docking process

As a critical element of the viral replication machinery, RdRp contains an active site composed of several key amino acid residues that interact with nucleotides during the RNA polymerization process. Identification and understanding of these residues are crucial for elucidating the enzyme's catalytic mechanism and for guiding the design of therapeutic agents or inhibitory compounds capable of suppressing RdRp activity.

RNA-dependent RNA polymerase (RdRp) plays a crucial role in the machinery that replicates viruses, featuring an active site made up of several vital amino acid residues that directly engage in the RNA polymerization process. The identification and understanding of these residues are crucial for elucidating the catalytic mechanism of the enzyme and for providing a foundation in the rational design of antiviral agents or therapeutic compounds capable of inhibiting RdRp activity.

According to the molecular docking findings shown in Table 1, the eight carotenoid substances found in Pandanus conoideus displayed a positive binding affinity for SARS-CoV-2 RdRp. Although their binding energy values were less favorable than those of the native ligand and the reference ligand, Remdesivir, several carotenoids formed interactions with key catalytic residues within the RdRp active site, particularly Ser759 and Asp760. These interaction patterns suggest that the carotenoids are capable of occupying the catalytic pocket and establishing molecular contacts that may influence ligand–protein recognition.

The catalytic site of SARS-CoV-2 RdRp consists of several conserved amino acid residues that are essential for viral RNA synthesis. Among these, Ser759 and Asp760 form part of the catalytic motif and play critical roles in nucleotide incorporation and phosphodiester bond formation during RNA replication. These residues have been widely recognized as important targets for antiviral compounds because ligand interactions at these positions may interfere with the polymerase catalytic process (Kushwaha et al., 2021; Pirzada et al., 2021). In the current research, the analysis of interactions mainly concentrated on Ser759 and Asp760, since these amino acids were repeatedly found to participate in hydrogen bonding with the docked carotenoid compounds. While other stable residues like Asp618 and Lys621 are known to play a role in RdRp function, the current docking results did not show any notable interactions with these residues.

This absence of hydrogen bonding may be attributed to the orientation and spatial positioning of these ligands within the binding cavity, which likely favor hydrophobic or π–π stacking interactions over polar contacts. Such alternative non-covalent interactions can still contribute to the overall stability of the ligand–protein complex, although they may not provide the same level of specificity or catalytic interference as hydrogen bonds.

On the other hand, a number of carotenoid compounds established well-oriented hydrogen bonds with the important catalytic residues in the SARS-CoV-2 RdRp active site, including Ser759 and Asp760. These interactions, along with hydrophobic and van der Waals contacts, may support sustained ligand binding and raise the possibility of interfering with the enzyme's catalytic activity. Although some carotenoids exhibited favorable interaction profiles, molecular docking alone cannot establish inhibitory potency or superiority over the reference ligand, Remdesivir, or the native ligand. In order to confirm their binding stability and antiviral efficacy, these compounds should be considered potential candidates for more research using molecular dynamics simulations and experimental investigations.

Cryptocapsin showed a unique interaction profile among the carotenoid compounds, according to the molecular docking results shown in Table 1 and the interaction visualizations in Figure 3. Although Capsanthin 3,6-epoxide exhibited a slightly more favorable binding energy (−6.755 kcal/mol), its hydrogen-bonding interaction was limited to Asn691. In contrast, Cryptocapsin formed hydrogen bonds with the catalytic residues Ser759 and Asp760, which are directly involved in the catalytic activity of SARS-CoV-2 RdRp. Interestingly, under the present docking conditions, neither the native ligand nor Remdesivir formed hydrogen bonds with these catalytic residues, despite exhibiting more favorable overall binding energies.

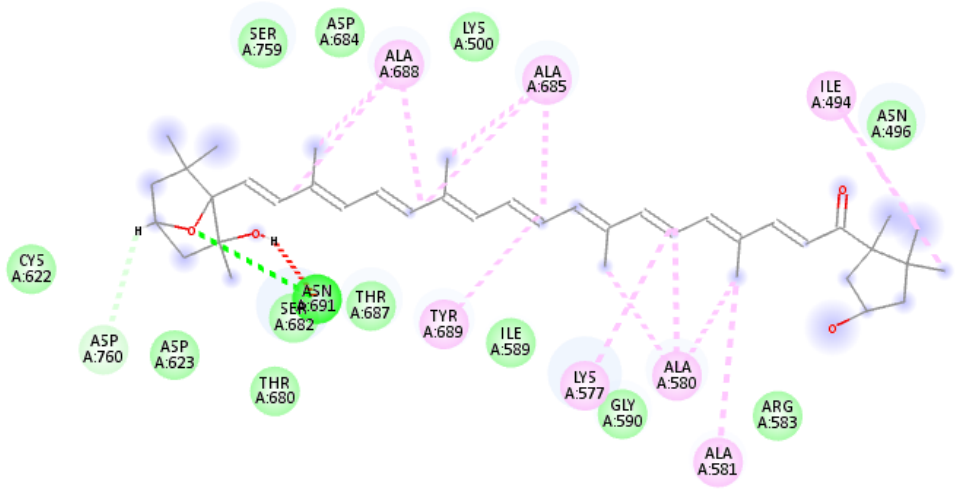
Table 1. Molecular docking results of carotenoid compounds and reference drugs against SARS-CoV-2 RdRp.

No	Carotenoid compounds	Binding energy (kcal/mol)	Contacting receptor residues
1	5,6-diepicapsokarpoxanthin	- 6.014	Ile494 Asn496 Leu576 Lys577 Ala580 Ala581 Ile589 Gly590 Cys622 Asp623 Ser682 Asp684 Ala685 Thr687 Ala688 Tyr689 Asn691 **Ser759 Asp760**
2	Capsorubin	- 6.288	Ile494 Asn496 Lys500 Leu576 Lys577 Ala580 Ala581 Ile589 Cys622 Asp623 Thr680 Ser682 Asp684 Ala685 Thr687 Ala688 Tyr689 Asn691 **Ser759 Asp760**
3	Capsanthin 5,6-epoxide	- 6.090	Ile589 Gly590 Thr591 Ser592 Phe594 Tyr595 Asp623 Thr680 Ser682 Thr687 Ala688 Tyr689 Asn691 Leu758 **Ser759 Asp760** Met924 Thr929
4	Capsanthin 3,6-epoxide	- 6.755	Ile494 Asn496 Lys500 Lys577 Ala580 Ala581 Arg583 Ile589 Gly590 Cys622 Asp623 Thr680 Ser682 Asp684 Ala685 Thr687 Ala688 Tyr689 Asn691 **Ser759 Asp760**
5	Capsanthin	- 6.478	Ile494 Asn496 Lys500 Leu576 Lys577 Ala580 Ala581 Ile589 Cys622 Asp623 Thr680 Ser682 Asp684 Ala685 Thr687 Ala688 Tyr689 Asn691 **Ser759 Asp760**
6	Cryptocapsin	- 6.466	Ile494 Asn496 Lys500 Lys577 Ala580 Ala581 Arg583 Ile589 Gly590 Cys622 Asp623 Thr680 Ser682 Asp684 Ala685 Thr687 Ala688 Tyr689 Asn691 **Ser759 Asp760**
7	β-cryptoxanthin 5,6-epoxide	- 6.023	Ile589 Gly590 Thr591 Ser592 Lys593 Phe594 Tyr595 Asp623 Thr680 Ser682 Thr687 Ala688 Asn691 Leu758 **Ser759 Asp760** Cys813 Met924 Thr929
8	Cryptoxanthin	- 6.407	Ile589 Gly590 Thr591 Ser592 Lys593 Phe594 Tyr595 Cys622 Asp623 Thr680 Ser682 Thr687 Ala688 Asn691 Leu758 **Ser759 Asp760** Met924 Thr929
9	Remdesivir	- 7,371	Ile 494 Val 495 Asn 496 Asn 497 Lys 500 Arg 569 Gln 573 Leu 576 Lys577 Ala580 Ile589 Gly590 Thr591 Ala685 Ala688 Tyr689 Leu758
10	Native ligand	- 8.742	Ile494 Val495 Asn496 Asn497 Asp499 Lys/500 Ser501 Lys545 Val557 Arg569 Gln573 Leu576 Lys577 Ala580 Gly590 Ser682 Gly683 Ala685 Tyr689

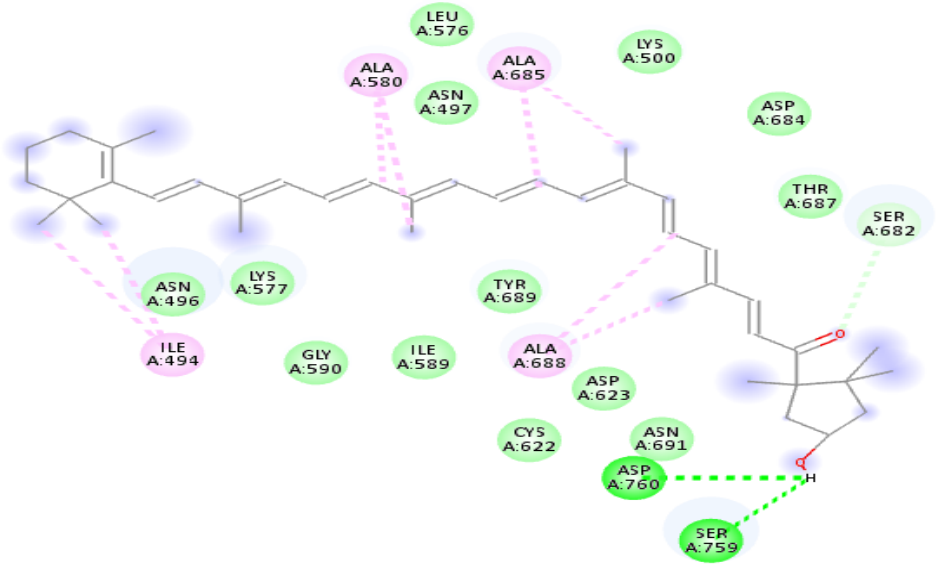
Note: Bold text denotes key catalytic residues discussed in this study

This finding suggests that Cryptocapsin adopts a different binding mode that enables direct interactions with catalytically important residues. Nevertheless, because molecular docking provides only a static prediction of ligand–protein interactions, these interaction patterns should not be interpreted as evidence of superior inhibitory activity. Further molecular dynamics simulations and biochemical assays are required to determine whether the observed interactions translate into stable binding and functional inhibition of RdRp.

Although ligand anchoring within the RdRp catalytic pocket may be facilitated by the hydrogen bonds generated between the ligand and the amino acid residues Asp760 and Ser759, enzymatic inhibition cannot be verified without molecular dynamics and experimental testing. By ensuring that the ligand stays anchored inside the active site to successfully block enzyme function, these interactions help to stabilize the ligand–receptor complex. Moreover, hydrogen bonding enhances the binding specificity of the ligand toward RdRp. At these strategically important positions involved in RNA polymerase catalysis, Asp760 and Ser759 are thought to interfere with the normal catalytic process, either by inducing conformational changes in the active site or by blocking access to the RNA substrate.



(a)



(b)

Figure 3. 2D Visualization of the interaction between ligands and the receptor: (a) Capsanthin 3,6-epoxide; (b) Cryptocapsin

Figure 4 illustrates the hydrogen bond distances formed between the ligand (cryptocapsin) and its receptor. The first hydrogen bond is observed at a distance of 2.73 Å, where the oxygen atom of Asp760 acts as a hydrogen bond acceptor, with an interaction energy of 25.00 kJ/mol (Black circle). The second hydrogen bond is formed at a distance of 2.33 Å, in which the oxygen atom of Ser759 serves as the hydrogen bond acceptor, with an interaction energy of 9.47 kJ/mol (yellow circle). It is well established that hydrogen bonds are typically formed when the distance between donor and acceptor atoms is ≤ 3.5 Å (Zhang and Aires-de-Sousa, 2007), confirming that both interactions identified in this study fall within the acceptable range for strong and stable hydrogen bonding (Zhang and Aires-de-Sousa, 2007; Zhou and Wang, 2019).

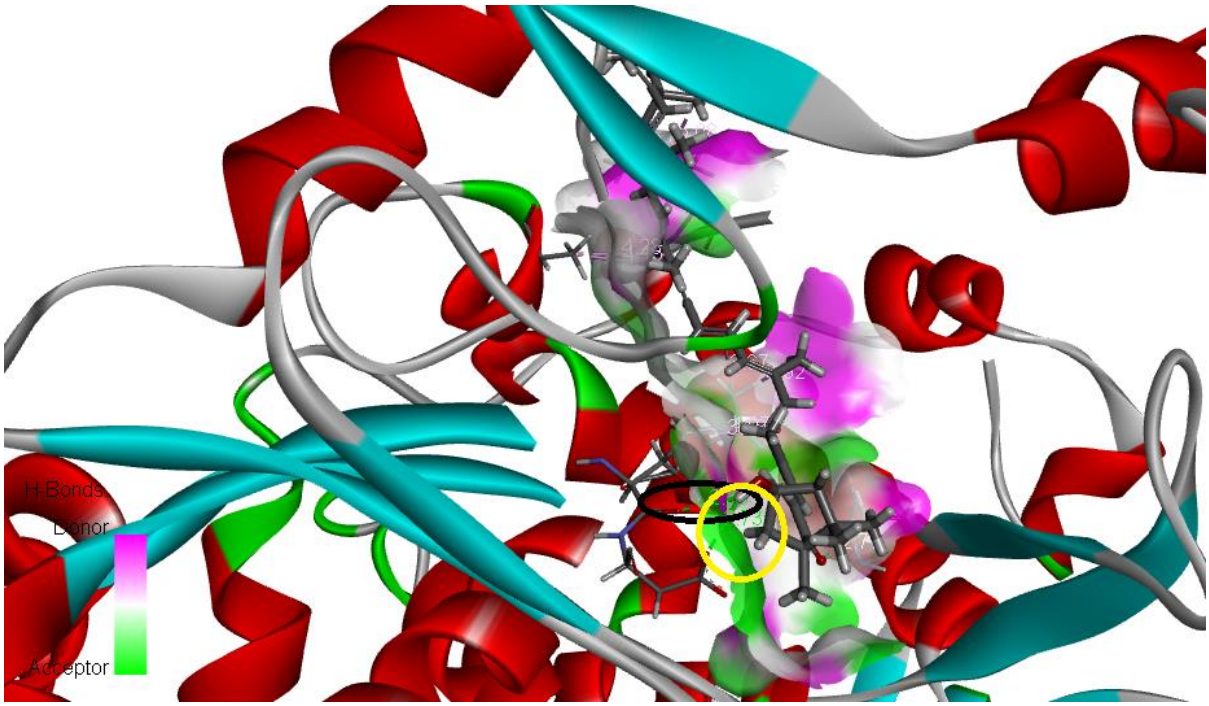


Figure 4. Visualization of interactions between the ligand (cryptocapsin) and the receptor.

Conclusion

Using an in silico molecular docking method, this study offers molecular insights into the interactions between carotenoids from Pandanus conoideus Lam. and SARS-CoV-2 RNA-dependent RNA polymerase (RdRp). Although their projected binding energies were lower than those of the native ligand and the reference ligand, Remdesivir, all assessed carotenoid compounds showed good binding inside the RdRp active region. By forming hydrogen bonds with the catalytic residues Ser759 and Asp760, Cryptocapsin demonstrated the most biologically relevant interaction profile among the tested compounds. In contrast, Capsanthin 3,6-epoxide demonstrated the most favorable binding energy but interacted primarily with a non-catalytic residue. These findings suggest that the evaluation of potential RdRp ligands should consider both predicted binding energy and the biological relevance of ligand–residue interactions within the catalytic pocket.

Overall, this study highlights the value of *Pandanus conoideus* as a tropical source of bioactive carotenoids for molecular interaction studies and early-stage antiviral screening. Nevertheless, the present findings are based solely on molecular docking predictions and therefore require further validation through molecular dynamics simulations, ADMET profiling, and experimental studies to confirm binding stability and biological activity.

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