ACTA VETERINARIA INDONESIANA
P-ISSN 2337-3202, E-ISSN 2337-4373

Penelitian Vol. 11, No. 1: 43–50, Maret 2023

Edible Bird's Nest as Potential Food with Anti-Viral and Anti-Inflammatory Properties Against Covid-19: an in Silico Study

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Diterima 7 Januari 2022, Disetujui 20 Desember 2022

ABSTRACT

The Chinese believe consuming edible bird's nests (EBN) can increase immunity to various diseases, including Covid-19. This study attempts to identify SARS COV-2-specific anti-viral and anti-inflammatory agents of EBN. We gathered samples from PubChem and Protein Data Bank (PDB). Afterwards, drug likeness was examined using the Lipinski model from the SCFBIO online service. The PASS web server analyzed the bioactive likelihood of chemicals found in EBN. Using PyRx 0.8 software with the blind docking technique. The PoseView web server and PyMol v2.4.1 software were utilized to ascertain molecular interactions. The in silico results show the potential of EBN as food therapy for Covid-19 sufferers, which is indicated by the presence of bioactive compounds from edible bird's nest consisting of 9-O-acetylated GD3, glycopeptide, N-acetyl neuraminic acid, N-glycolyl-neuraminic acid, sialic acid, and tetra acetyl-thymol-beta-D-glucoside. These bio compounds are predicted to work as anti-viral and anti-inflammatory candidates against SARS-COV-2.
Keywords: Edible bird's nest, in silico, molecular docking, 3D visualization, SARS COV-2.

ABSTRAK

Masyarakat Tionghoa percaya bahwa dengan mengkonsumsi sarang burung walet (SBW) dapat meningkatkan kekebalan tubuh terhadap berbagai penyakit, termasuk Covid-19. Penelitian ini bertujuan untuk mengidentifikasi agen anti-virus dan anti-inflamasi spesifik terhadap SARS COV-2 yang terkandung di dalam SBW. Sampel dikoleksi dari PubChem dan Protein Data Bank (PDB) yang selanjutnya dilakukan pemeriksaan *drug likeness* menggunakan model Lipinski dari layanan online SCFBIO. Kemungkinan bioaktif bahan kimia yang ditemukan dalam SBW dianalisis menggunakan server web PASS. Teknik *blind docking* digunakan dalam penelitian ini menggunakan perangkat lunak PyRx 0.8. Interaksi molekuler juga dianalisis dalam penelitian ini menggunakan server web PoseView dan perangkat lunak PyMol v2.4.1. Hasil studi in silico menunjukkan adanya potensi SBW sebagai terapi makanan bagi penderita Covid-19, yang ditunjukkan dengan adanya senyawa bioaktif dari sarang burung walet yang terdiri dari 9-O-acetylated GD3, glycopeptide, N-acetyl neuraminic acid, N- asam glikolyl-neuraminic, asam sialat, dan tetra asetil-timol-beta-D-glukosida. Senyawa bio tersebut diprediksi dapat bekerja sebagai kandidat anti virus dan anti inflamasi terhadap SARS-COV-2.
Kata Kunci: sarang burung walet, *in silico*, *molekuler docking*, visualisasi 3D, SARS COV-2

INTRODUCTION

Edible bird's nest is a food of animal origin believed in providing many benefits for beauty and health. Currently, the efficacy of the anti-viral and anti-inflammatory properties of EBN is increasingly studied due to the rising number of COVID-19 cases worldwide. The previous study (Haghani *et al.,* 2017) successfully compared EBN's anti-viral efficacy to that of commonly prescribed anti-viral medications such as oseltamivir and amantadine by reducing viral proteins such as Rab5 and all proteins involved in actin filament polymerization such as RhoA. EBN can inhibit viral hemagglutination (HA) activity (Nuradji *et al.,* 2018). Anti-viral medications to treat the Influenza A virus (IAV) that are frequently utilized include baloxavir, which inhibits the production of viral mRNA (Koszalka *et al.,* 2017), oseltamivir, zanamivir, and peramivir by selective neuraminidase inhibitors (Hama 2015), and favipiravir by inhibiting RNA polymerase activity (Furuta *et al.,* 2013). However, the combined efficacy of edible bird nest therapy with anti-viral drugs has not been studied.

Additionally, EBN can reduce pro-inflammatory cytokines and chemokines such as TNF-, CCL-2, NF-, NO, and IL-6, and increase IFN-γ (Haghani *et al.,* 2016) is often referred to as the cytokine storm phenomenon, which COVID-19 sufferers fear the most. In addition, EBN also ameliorates apoptosis (Yew *et al.,* 2014) and normalizes the cellular shape of IAV-infected cells (Haghani *et al.,* 2017). Thus, ingesting EBN during severe illness can lessen collateral harm to host cells. Moreover, EBN has antibacterial properties (Zhao *et al.,* 2016). Its enhances B cell function, increasing protection against opportunistic bacterial infections in immunosuppressed patients with terminal illnesses. However, the efficacy of EBN as an anti-viral and anti-inflammatory agent has not been experimentally compared with anti-inflammatory medications utilized in clinical practice. The in silico computational methodology is an efficient and cost-effective tool for demonstrating the anti-viral and anti-inflammatory properties of EBN. Therefore, this study determine the anti-viral and anti-inflammatory properties of EBN.

This results will give benefit health experts and COVID-19 researchers, EBN consumers and suppliers. Researchers require this information to determine why Chinese people believe consuming EBN will hasten the recovery of COVID-19 patients.

MATERIALS AND METHODS

Sample

This study used chemical compounds from white edible bird nests consisting of 9-O-acetylated GD3 (CID 73427362), glycopeptide (CID 56928060), N-acetyl neuraminic acid (CID 439197), N-glycolyl-neuraminic acid (CID 440001), ovotransferrin (CID 145708002), sialic acid (CID 906), and tetra acetyl-thymol-beta-D-glucoside (CID 14239370) (Chua *et al.,* 2021). Afterwards, control drugs such as PF-07321332 (paxlovid) or control 1 (CID 155903259) and molnupiravir or control 2 (CID 145996610) were utilized. Samples were acquired by using the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). This database stores compound ID, canonical SMILE, and compound 3D structure. The PubChem database is a specific database for storing chemical compounds of artificial materials, organics, and substances (Kim *et al.,* 2016). Helicase (PDB ID: 6ZSL), Mpro (PDB ID: 6Z2E), spike (GDP ID: 6LZG), and NFKB1 (4G3D) 3D structure of the complete protein were the target proteins for the SARS-CoV-2 anti-viral and anti-inflammatory agents used in this study. Targets were extracted in PDB format from the Protein Databank database (https://www.rcsb.org) (Ugwu *et al.,* 2018; Widowati *et al.,* 2020).

Docking simulation

Interaction simulation between bioactive chemicals from EBN and helicase, Mpro, spike, and NFKB1 proteins was performed utilizing the blind docking approach and PyRx 0.9.9 software (Scripps Research, USA) with an academic license. Molecular docking is a method that plays a role in carrying out molecular interactions through specific software and identifying the patterns of molecular interactions that are formed. The binding energy created under constant temperature and pressure conditions resulting from molecular docking is binding affinity (kcal/mol) with a negative value. The objective of blind docking is to determine the binding energy of putative ligands that elicit response from the target protein. AutoGrid with a blind docking method is arranged to cover all target protein domains to achieve perfect binding (Nugraha *et al.,* 2021).

Chemical interaction analysis

Identification of chemical interactions obtained from molecular docking simulations was carried out using LigPlus+ v.2.2.4 software (EMBL-EBI, Wellcome Trust Genome Campus, Hinxton, UK), which works based on Java programming algorithms. The program exhibits weak bond types, such as hydrogen and hydrophobic. These two weak interactions are formed to stabilize ligand binding to the target protein domain and trigger the activation of biological responses (Susanto *et al.,* 2018).

Molecular dynamic and 3D visualization

Molecular dynamic simulation using CABS-flex 2.0 (http://biocomp.chem.uw.edu.pl/CABS-flex2/index) was used to determine the bond stability of the docked molecular complex. Parameters used for identification included rigidity, temperature range, C -alpha restraints, RNG seed, cycles between trajectory, and global weight. The simulation results on the CABS-flex 2.0 version refer to the root-mean-square fluctuation (RMSF) value which must have a value of 1-3 (Wijaya *et al.,* 2021). Molecular complexes of the docking simulation result are displayed in 3D through structural selection and staining stages with software PyMOL 2.5.2 version (Schrödinger, Inc., New York, NY, USA) with an academic license (Prahasanti *et al.,* 2021).

RESULTS

The activity of bioactive compounds from edible bird nest

Chemical compounds from EBN such as 9-O-acetylated GD3, glycopeptide, N-acetyl neuraminic acid, N-glycolyl-neuraminic acid, ovotransferrin, sialic acid, and tetra acetyl-thymol-beta-D-glucoside are predicted to bind into viral proteins with varying binding affinity values. Bioactive chemicals that found in EBN include 9-O-acetylated GD3, glycopeptide, N-acetyl neuraminic acid, N-glycolyl-neuraminic acid, ovotransferrin, sialic acid, and tetra acetyl-thymol-beta-D-glucopyranoside (Figure 1). These bioactive compounds acted as ligands in this study. In addition, the CID, weight, Canonical SMILE, molecular formula, and citation for each target molecule were obtained from PubChem (https://pubchem.ncbi.nih.gov/). This study also used the control drug as a comparison (Table 1 and Table 2). The 3D structure of chemical compounds in EBN was visualized through PyMol software. The compounds were displayed in stick structure with coloring selection based on the constituent atoms.

The ligand's 3D structure in pdb format was derived via minimization using the OpenBabel PyRx plugin. After obtaining the protein's 3D structure from the RCSB PDB database (https://www.rcsb.org/), the water molecules were removed from the target protein to determine the binding value with the highest affinity. The docking process in this study used AutoGrid with positions Mpro: Center (Å) X: -26,283 Y: 12,599 Z: 58,965 Dimension (Å) X: 66,125 Y: 72,942 Z: 51,456. Spike RBD: Center (Å) X: -32,325 Y: 25,812 Z: 21,076 Dimension (Å) X: 48,156 Y: 47,576 Z: 56,346. Helicase: Center (Å) X:-13,606 Y: 25,925 Z: -70,215 Dimension (Å) X: 89,527 Y: 89,878 Z: 99,159. NFKB1: Center (Å) X:42.46 Y:14.68 Z:38.03 Dimension (Å) X:90.70 Y:67.39 Z:51.93 in PyRx software. AutoGrid in this study was directed to cover the entire protein surface because the docking method used was a blind docking type. The docking results showed that the 9-O-acetylated GD3 compound had more negative binding affinity than the other compounds and also the four control drugs. However, the other compounds had more negative binding energy value than the control but weaker binding energy than 9-O-acetylated GD3 (Table 2). Molecular binding of the 9-O-acetylated GD3 molecule can change target protein inhibitory activity , which consists of Mpro, Spike, Helicase, and NFKB1. This interaction is projected to result in anti-viral and anti-inflammatory responses. The PyMol 2.5 program displays the 3D structure molecular docking simulation results for the molecular complex with lowest binding affinity value as a cartoon structure on transparent surfaces for the target protein (blue) and ligands with sticks (green) (Figure 2).

Molecular interaction and bond stability bioactive compounds of edible bird nest with target proteins

Molecular interactions consisting of hydrogen and hydrophobic bonds in the docking complex were identified through LigPlus+ software. The results (Figure 3) showed that the 9-O-acetylated GD3 compound with the Mpro domain through hydrogen bonds at positions Glu290, Arg131, and Thr199 and hydrophobic at Leu287, Lys137, Leu286, Tyr239, Lys5, Gly138, Asp289, Leu272, Tyr126, Glu288, Ser139, Leu271, and Tyr237, in the spike domain via hydrogen bonding at positions Ser541, Pro463, Arg355, Glu516, and Phe515 and hydrophobic at Leu390, Phe392, Ala462522, Phe464, Leu517, Cys391, Arg466, Glu465, and Thr430, in the helicase domain via hydrogen bonds with positions Arg22, Arg21, Glu136, and Ser236 and hydrophobic at Val241, Val232, Arg129, Asn9, Pro242, Pro234, Phe133, Glu128, Leu240, Phe24, Leu132, Pro238, and Tyr277, the ligand-binding position in the M^{pro}, helicase, and spike domains could be used as a target recommendation for SARS-CoV-2 anti-viral candidates. The 9-O-Acetylated GD3 bond was also formed in the NFKB1 domain through hydrogen bonds at the Asp121 and Ser113 positions. It was hydrophobic at Leu143, Cys119, Arg59, Pro65, Thr159, Arg157, Val61, Ile142, Ala156, Gly116, Gly116, Gly64, Gly68, Glu155, Gly141, Val115, and His67. Position ligand binding on the NFKB1 domain can be used as recommendation for candidate anti-inflammatory targets. This study used

a CABS-flex 2.0 web server with rigidity parameters: 1.0, temperature range: 1.40, C-alpha restraints: 1.0, RNG seed: 8204, cycles between trajectory: 150, and global weight: 1.0. The results showed that the RMSF value in the pocket-binding domain of the Mpro_9-O-Acetylated GD3 complex had an average of 2, ≥2 spike_9-O-acetylated G3, 1 helicase_9-O-acetylated GD3, and 1.5 NFKB1_9- O-acetylated GD3 (Fig. 3). The overall RMSF value of the docked complex showed stable fluctuations in generating molecular interactions and allowed for in silico validation of effective anti-viral and anti-inflammatory candidates.

DISCUSSION

Edible bird's nest is food of animal origin which is popular among Chinese people because this superfood has a delicious taste and is highly nutritional. In addition, they believe that EBN could improve health. In the case of the Covid-19 outbreak, demand for EBN surged because they were thought to reduce the severity of symptoms of Covid-19 sufferers. Ccomposition of EBN is necessary understanding to explain why it is consumed as food therapy for Covid-19 sufferers. The natural protein composition found in EBN in this study, shows the potential for anti-viral and anti-inflammatory properties that Covid-19 sufferers greatly need.

A comparison of binding affinity values between chemical compounds from EBN and control drugs can be seen based on the analysis data (Table 2). Almost all bioactive compounds from EBN have more negative binding affinity values than the control drugs for anti-viral drugs (PF-07321332 and molnupiravir). Only the ovotransferrin compound has more positive binding affinity value than the two controls. Nonetheless, the overall bioactive compounds from the EBN also had more negative binding energy than the control anti-inflammatory drugs (ibuprofen and diclofenac sodium).

Binding affinity is the energy created by the interaction of two molecules, such as ligands and proteins, which results in binding (Wijaya *et al.,* 2021). Also, it enables to make a contact of the docked molecule complex, which, in a closed system, operates according to the principles of thermodynamics and has a negative value (Luqman *et al.,* 2020). Ligands with the most negative binding affinity values can potentially affect the activity of target proteins, such as inhibitors (Kharisma *et al.,* 2021). The interaction of chemical bonds formed has a type: weak bonds such as hydrophobic and hydrogen. These bonds play a role in the ligand's stability and ability to trigger the target protein's activity (Widyananda *et al.,* 2021).

The receptor binding domain (RBD) functional domain is present on the spike protein of SARS-CoV-2, which participates in the attachment process. Ideally, this domain is a binding target for drug-candidate compounds (Huang *et al.,* 2020). Helicase, or NSP13 is the essential protein in the SARS-CoV-2 replication process, with a high abundance of conserved sequences, and viral assembly is played by the viral protease Mpro (Wu *et al.,* 2020). In the case of COVID-19, there are conditions in which immune cells produce excessive cytokines or a cytokine storm, which causes systemic inflammation during SARS-CoV-2 infection (Ahmed 2021). The protein activity of pro-inflammatory agents such as NFKB1 is vital in triggering cases of cytokine storm in COVID-19 patients to death. When SARS-CoV-2 infection occurs, it can initiate NFKB1 activation to transcribe genes encoding TNF-alpha, IFN-gamma, IL-6, and IL-1. These three proteins can exacerbate inflammatory conditions in COVID-19 patients. This indicates that NFKB1 can be a binding target for anti-viral candidate chemical compounds (Mukund *et al.,* 2019).

Based on the results of this study, bioactive compounds from edible bird's nests consisting of 9-O-acetylated GD3, glycopeptide, N-acetyl neuraminic acid, N-glycolyl-neuraminic acid, sialic acid, and tetra acetyl-thymol-beta-D-glucoside are predicted to be able to work as anti-viral candidates through a direct binding mechanism with viral proteins consisting of a spike, helicase, and Mpro, because these six compounds have more negative binding affinity values than control drugs and are stable, with fluctuations below 3. However, all bioactive chemicals in EBN are prospective anti-inflammatory options since their binding affinity to NFKB1 is lower than that of the control medication. The interaction in the molecular complex tends to be stable, with fluctuations below 3. Overall, chemical compounds from EBN can form weak bond interactions, such as hydrogen and hydrophobicity. These interactions can strengthen the apparent effect of inhibitor activity produced when binding to the target. In summary, this study revealed the dual inhibitor concept, which refers to the capacity of chemical compounds from edible bird's nests to act as anti-viral and anti-inflammatory candidates. This may result in anti-viral and anti-inflammatory responses. To increase the efficacy of bioactive substances from edible bird's nests, the results of this study must be verified by further testing methods, such as *in vitro* and *in vivo*.

Table 1. Results sample preparation of edible bird nest bioactive compounds using PubChem.

Compound	CID	Canonical SMILE	Weight (g/mol)	Molecular Formula
9-O-Acetylated GD3	73427362	CCCCCCCCCCCCCC=CC(C(COC1C(C(C(C(O1)CO)OC2C(C(C(C(O2)CO)O)OC3(CC(C(C(O3)C(C(CO)OC4(CC(C(C(O4)C(C(COC(=O)C)O)O)NC(=O)C)O)C(=O)O)O)NC(=O)C)O)C(=O)O)O)O)O)NC(=O)C)O	1290.4	$C_{56}H_{95}N_3O_{30}$
Glycopeptide	56928060	CCNC1C(C(C(OC1O)CO)OC2C(C(C(C(O2)CO)O)O)NC(=O)C)OC(C)C(=O)NC(C)C(=O)NC(CCC(=O)NC(CCCCN)C(=O)NC(C)C(=O)O)C(=O)N	880.9	$C_{36}H_{64}N_8O_{17}$
N-acetyl neuraminic acid	439197	CC(=O)NC1C(CC(OC1C(C(CO)O)O)(C(=O)O)O)O	309.27	$C_{11}H_{19}NO_9$
N-glycolyl-neuraminic acid	440001	C1C(C(C(OC1(C(=O)O)O)C(C(CO)O)O)NC(=O)CO)O	325.27	$C_{11}H_{19}NO_{10}$
Ovotransferrin	145708002	CC(C)CC(C(=O)O)NC(=O)C(CO)NC(=O)C1CCCN1C(=O)C(C(C)C)NC(=O)C(CCCN=C(N)N)N.C(=O)(C(F)(F)F)O	684.7	$C_{27}H_{47}F_3N_8O_9$
Sialic acid	906	CC(=O)NC1C(CC(OC1C(C(CO)O)O)(C(=O)O)O)O	309.27	$C_{11}H_{19}NO_9$
Tetraacetyl-thymol-beta-D-glucoside	14239370	CC1=CC(=C(C=C1)C(C)C)OC2C(C(C(C(O2)COC(=O)C)OC(=O)C)OC(=O)C)OC(=O)C	480.5	$C_{24}H_{32}O_{10}$

Table 2. Simulation molecular docking of compounds results and target protein control.

Compound	Minimize Energy (kcal/mol)	Binding Affinity (kcal/mol)			
		Mpro	Spike	Helicase	NFKB1
9-O-Acetylated GD3	+264309.69	-9.3	-9.9	-10.4	-9.0
Glycopeptide	+72860.15	-8.2	-6.9	-9.5	-7.4
N-Acetyl neuraminic acid	+248.95	-6.1	-5.3	-7.1	-5.4
N-Glycolyl-neuraminic acid	+269.81	-6.0	-5.4	-6.3	-5.4
Ovotransferrin	+11241.27	-5.2	-4.9	-5.2	-4.6
Sialic acid	+16788.47	-7.7	-7.7	-9.5	-7.3
Tetraacetyl-thymol-beta-D-glucoside	+304.00	-7.7	-6.1	-7.1	-5.9
Control 1 (PF-07321332/Paxlovid)	+1831.35	-6.6	-6.6	-7.5	-
Control 2 (Molnupiravir)	+323.65	-6.7	-6.2	-7.4	-
Control 3 (Ibuprofen)	+206.28	-	-	-	-5.4
Control 4 (Diclofenac Sodium)	+296.14	-	-	-	-5.6

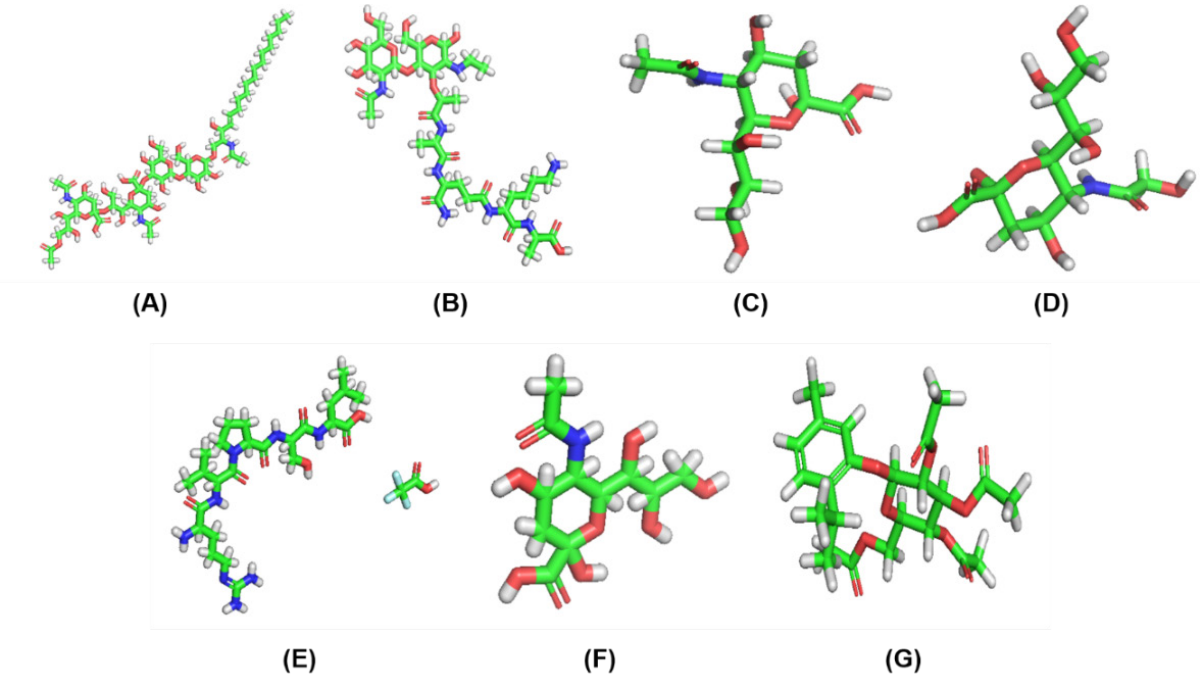

Figure 1. 3D structure of the compound edible bird nest content. (A) 9-O-Acetylated GD3; (B) Glycopeptide; (C) N-acetyl neuraminic acid; (D) N-glycolyl-neuraminic acid; (E) Ovotransferrin; (F) Sialic acid; and (G) Tetraacetyl-thymol-beta-D-glucoside.

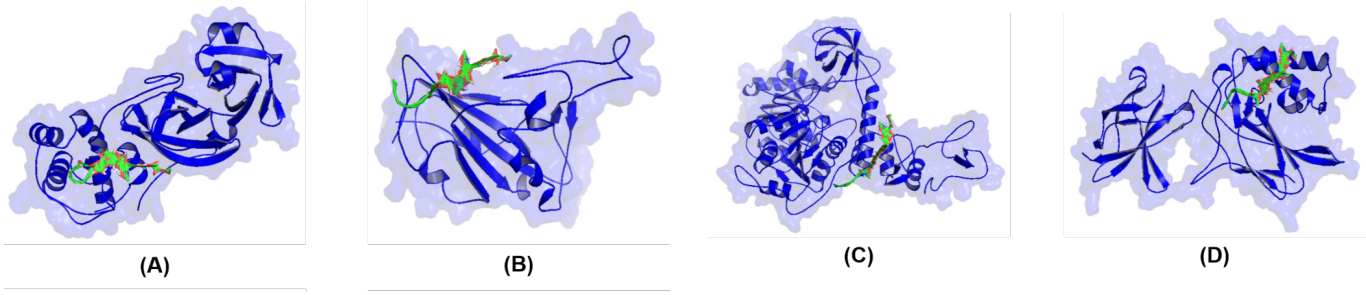

Figure 2. 3D visualization of molecular docking simulation results. (A) M^{pro}_9-O-Acetylated GD3; (B) Spike_9-O-Acetylated GD3; (C) Helicase_9-O-Acetylated GD3; and (D) NFKB1_9-O-Acetylated GD3.

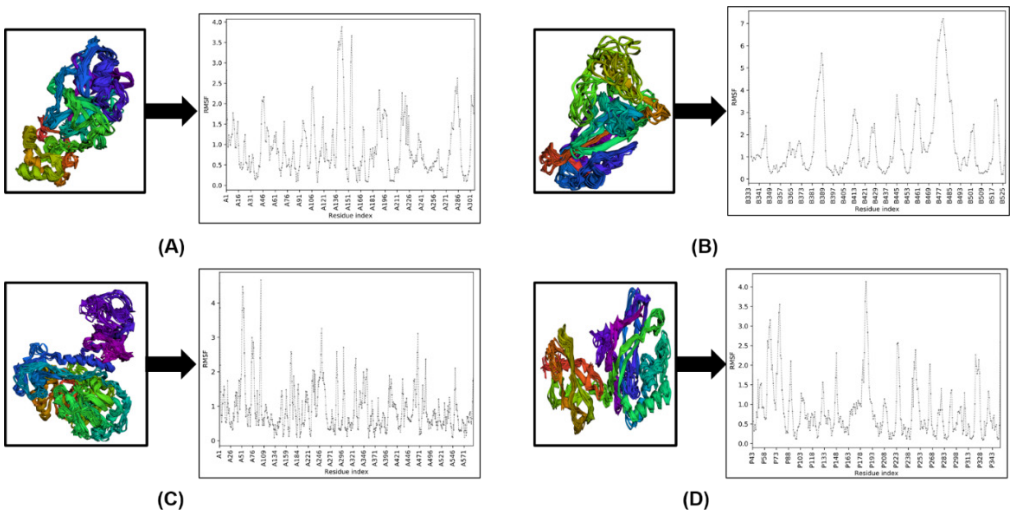

Figure 3. Molecular dynamic simulation of the 9-O-acetylated GD3 molecular complex with the target protein. (A) M^{pro}_9-O-acetylated GD3; (B) Spike_9-O-acetylated GD3; (C) Helicase_9-O-acetylated GD3; and (D) NFKB1_9-O-acetylated GD3.

ACKNOWLEDGMENT

The authors thank LPPM UWKS, Surabaya, Indonesia, for providing funds with Grant No. 105/LPPM/UWKS/IV/2022. We would like to thank Frances Sherwood-Brock for proofreading the manuscript to ensure correct English.

"The authors state that they have no known conflicting financial interests or personal ties that may be seen as having influenced the work described in this study."

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