ORIGINAL ARTICLE

Computational Approach of Molecular Docking of Ag85 Protein Complex from Mycobacterium tuberculosis against β2 integrin as the Development of Tuberculosis Vaccine Based on Secretory Protein

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ABSTRACT

Introduction: Tuberculosis is a chronic infectious disease caused by *M.tuberculosis*. BCG is currently the only type of tuberculosis vaccine recognized by the WHO. BCG vaccine has limited protection. The vaccines currently being developed can be derived from the secretory protein of a pathogen. One of the secretory proteins found in *M.tuberculosis* is the Ag85 complex. Proteins Ag85 complex binds to integrin β2 receptor in *M.tuberculosis* virulence. Therefore, this study aims to determine the potential for binding between the complex Ag85 protein and the receptor β2 integrin as an in-silico development of a secretory protein-based TB vaccine. **Methods:** This study is exploratory research with in silico testing. This study utilized the ClusPro website to perform molecular docking based on the binding energy values and the resulting binding interaction models. We obtained the structures of the Ag85 protein complex and integrin β2 via the Protein Data Bank website and visualized the binding interaction model using PyMOL software. **Results:** In this study, the binding energy values obtained for the three bonds between the Ag85 complex proteins with integrin β2 were negative, and all hydrogen bonds showed that the bonds formed were strong and stable. The lowest value is observed in the interaction between Ag85 B protein and β2 integrin. **Conclusion:** Ag85B-β2 integrin bond exhibits the most stable and spontaneous binding, as indicated by lowest binding energy. This interaction occurs at the active site of the amino acid.
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Keywords: *M.tuberculosis*, Ag85 complex, β2 integrin, TB vaccine

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INTRODUCTION

Tuberculosis (TB) is the leading cause of human death throughout the world (1). The World Health Organization (WHO) states that 10.6 million people in the world are affected by TB disease, with a death rate of 1.6 million people in 2021 (2). Tuberculosis is a chronic infectious disease caused by the *Mycobacterium tuberculosis* (*M.tuberculosis*) bacteria, spreading through respiratory, air, and droplet transmission from people infected with TB (3,4). Vaccination is one of the government's efforts to prevent TB transmission (5). Bacille Calmette-Guerin (BCG) is still the only TB vaccine recognized by WHO currently. The BCG vaccine is derived from an attenuated strain of *Mycobacterium bovis* (6). Although it protects against pulmonary TB in childhood, the BCG vaccine has several limitations in protecting against pulmonary TB in adults (7).

The BCG vaccine has a high risk of becoming malignant. The weakness of the current BCG vaccine is that a better vaccine is still needed to prevent TB transmission. The vaccines currently being developed can be derived from the secretory protein of a pathogen. Pathogenic secretory proteins are antigenic and capable of inducing a significant immunogenic response in the body. Thus, numerous vaccine candidates have been developed using a pathogen's secretory protein. The main secretory protein found in *M.tuberculosis* is the Ag85 complex (6,8,9). The complex Ag85 protein has three types of proteins, namely Ag85 A, Ag85 B, and Ag85 C (10,11). The complex Ag85 protein binds to the fibronectin (Fn) receptor in the adhesion process, maintaining cell wall

integrity in M. tuberculosis, allowing it to enter host cells, and facilitating bacterial colonization (10). The complex Ag85 protein has been shown to bind to Fn in M. tuberculosis virulence, allowing it to bind to other receptors such as integrins. Integrins serve as transducers that assist in transmission extracellular adhesion into intracellular signals, thereby causing cellular activities such as migration, spreading, and phagocytosis (12). Integrins functioning in bacterial migration activities, trigger protein recruitment, and strengthen cell adhesion are integrins β2, β3, and α5β1 (13). The β2 integrin pathway contributes to the modulation of macrophage survival, which is crucial for controlling *M.tuberculosis* infection. Therefore, this study aims to determine the potential for binding between the complex Ag85 protein and the integrin receptor β2, as an in-silico development of a secretory protein-based TB vaccine.

A new research method that utilizes computing and database technology to determine the potential of the Ag85 protein complex with integrin β2 in developing a secretory protein-based TB vaccine within silico testing using the molecular docking method. Molecular docking is a method of interaction between molecules based on the binding energy value of a stable bond complex. The lower the binding energy value, the easier it is for the ligand to form a complex with the receptor, implying that the bond formed will be more stable (14). Based on the explanation of the problems above, it is necessary to carry out further research on the potential of molecular docking of the M. tuberculosis Ag85 protein complex against integrins β2 as a means of developing a secretory protein-based tuberculosis vaccine.

MATERIALS AND METHODS

Receptor and Ligand Determination

We determined the receptors and ligands through several literature reviews of scientific articles or journals from NCBI (National Center of Biotechnology Information) and Google Scholar.

Receptor and Ligand Preparation

The receptors and ligands used in this study after going through the review process are the *M.tuberculosis* Ag85 A (PDB ID: 1SFR), Ag85 B (PDB ID: 1F0N), and Ag85 C (PDB ID: 1DQZ) proteins, and the β2 (PDB ID: 2P28) integrin receptor protein. We proceed with the download via the Protein Data Bank (PDB) by entering the PDB ID of each receptor and ligand in the PDB website search field. We documented the 3D structural data for the Ag85 protein complex, β2 integrins in Pdb format.

Molecular docking

We assess the molecular docking on the ClusPro website (https://cluspro.org/home.php). Select the "Result" column to see the results of the completed docking and review the docking results by pressing the ID code listed. The results of the docking process are binding energy values and binding interaction models between receptor-ligand. We analyzed the results based on the binding energy value. The lower the binding energy value, the more stable the protein binds.

Visualization of Docking Results

Subsequently, we visualized the bond complex with the smallest binding energy value from the docking results using PyMOL software downloaded via the official PyMOL website. The visualization then identifies the distance, amino acid residues, and bonds formed in the interaction. We captured the screenshots showing the binding site of the complex Ag85 protein and β2 integrin. Data presentation uses screenshots of images in molecular docking visualization and tables in Microsoft Word software.

Docking validation

We validated the docking results using Autodock vina Autodock Tools 1.5.7 to determine the amino acid residues on the active site between the receptor and the natural ligand. Docking validation can identify the similar amino acid residues between the test ligand and the natural ligand, which indicates the existence of similar types of interactions (15,16).

RESULTS

The lowest binding energy and binding interaction model between Ag85 A, Ag85 B, Ag85 C proteins and β2 integrin

The docking result via Cluspro web between Ag85A protein (PDB ID: 1SFR) with integrin β2 (PDB ID: 2P28) in the binding interaction model number 12 has the lowest binding energy value of -1036.0 and shows the most stable bond. The docking result between Ag85B protein (PDB ID: 1F0N) with integrin β2 (PDB ID: 2P28) in the binding interaction model number 0 has the lowest binding energy value of -1055.0 and shows the most stable bond. The docking result between Ag85C protein (PDB ID: 1DQZ) with integrin β2 (PDB ID: 2P28) in the binding interaction model number 6 has the lowest binding energy value of -962.0 and shows the most stable bond, as can be seen in Table I.

The binding interaction model number 12 between Ag85A protein and β2 integrin visualized using PyMOL software can be seen in Figure 1A. This visualization describes the type of bond, bond distance, and the most important amino acid residues involved in the interaction of Ag85 A protein with β2 integrin can be seen in Figure 1B and Table II. The bonds formed between Ag85 A and integrin β2 consist of 9 strong and stable hydrogen bonds. Of the 9 hydrogen bonds, only 1 bond is on the side binding antigen receptor of the amino acid residue GLN-494.

The binding interaction model number 0 between

Table I. Lowest binding energy values for Ag85 A, Ag85 B, and Ag85 C proteins with β2 integrin

Ligands	Receptor	Interaction Model Number	Lowest binding energy values
Ag85 A	Integrin β2	12	-1036.0
Ag85 B	Integrin β2	0	-1055.0
Ag85 C	Integrin β2	6	-962.0

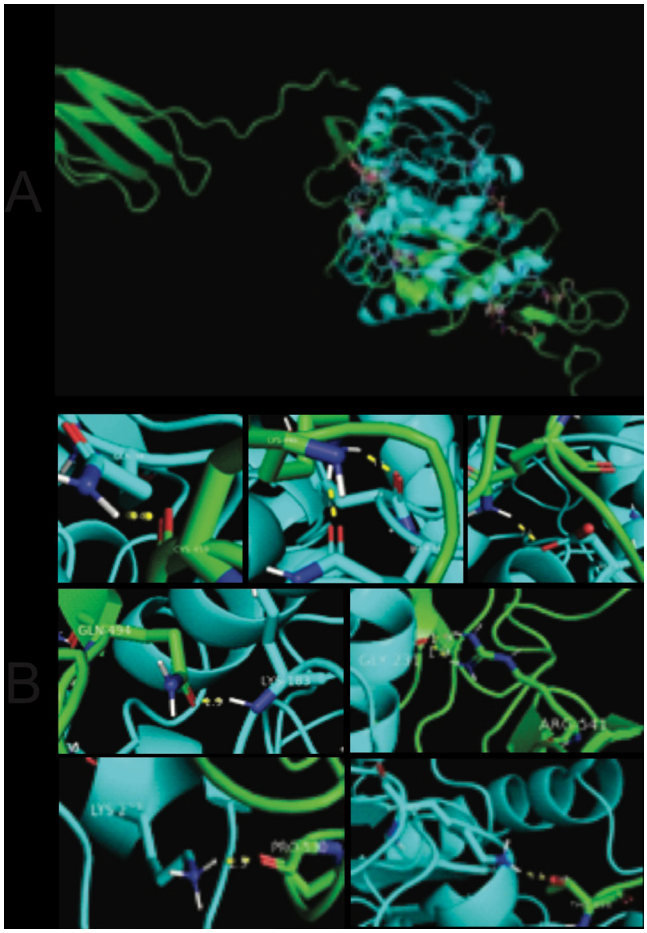

Figure 1: Interaction of amino acid residues between the *M. tuberculosis* Ag85 A protein and β2 integrin. (A). Cartoon diagram of the binding interaction model of 12 docking results between the Ag85 A *M. tuberculosis* protein and β2 integrin (B) The bond distance (E) indicates the bond between two amino acid residues. The dashed yellow line represents the distance between two amino acid residues that form hydrogen bonds. White – hydrogen, red – oxygen, and dark blue – nitrogen atoms. Ag85 A *M. tuberculosis* (cyan) and β2 integrin (green).

Table II. Binding and amino acid residues of the *M.tuberculosis* Ag85 A protein to β2 integrin

Type of bond formed	Total number of bonds	Bond distance (Å)	Strength	Amino acid residues linked between ligand and receptor		Active amino acid residues between β2 integrin and native ligand NAG401
				Ag85 A amino acid	β2 integrin amino acid	
Hydrogen bond	9	2,0 Å	Strength	GLN-84	CYS-459	CYS-535, VAL-526, CYS-495, GLY-509, GLN-510, GLN494, ALA-395, LEU-420
		1,7 Å	Strength	GLN-84	LYS-440	
		1,9 Å	Strength	LYS-227	PRO-530	
		1,7 Å	Strength	TYR-83	LYS-440	
		2,0 Å	Strength	ASP-185	GLN-462	
		1,9 Å	Strength	LYS-183	GLN-494	
		1,7 Å	Strength	LYS-89	THR-499	
		1,9 Å	Strength	GLY-231	ARG-541	
		1,9 Å	Strength	GLY-231	ARG-541	

Description: GLN, Glutamine; CYS, Cysteine; LYS, Lysine; PRO, Proline; TYR, Tyrosine; ASP, Aspartic Acid; THR, Threonine; GLY, Glysine; ARG, Arginine (Source: 17).

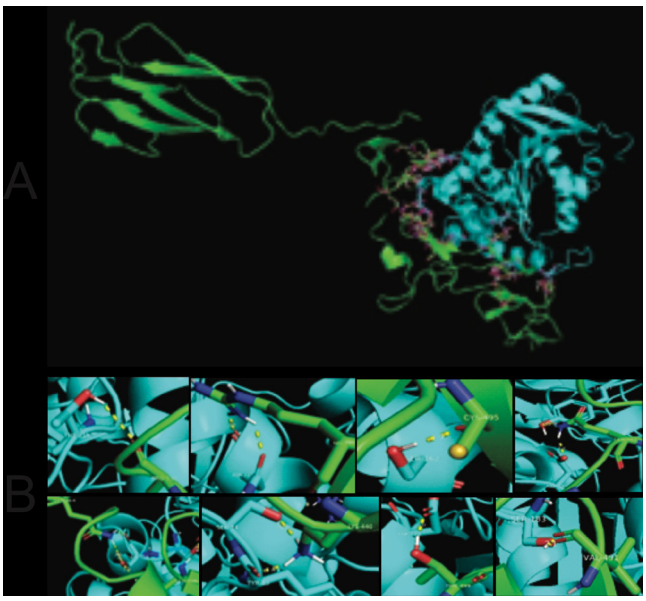

Figure 2: Interaction of amino acid residues between the *M. tuberculosis* Ag85 B protein and β2 integrin. (A). Cartoon diagram of the binding interaction model 0 resulting from docking between the Ag85 B *M. tuberculosis* protein and β2 integrin (B). The bond distance (E) indicates the bond between two amino acid residues. The dashed yellow line represents the distance between two amino acid residues that form hydrogen bonds. White – hydrogen, red – oxygen, and dark blue – nitrogen atoms. Ag85 B *M. tuberculosis* (cyan) and β2 integrin (green)

Ag85 B protein and β2 integrin visualized using PyMOL software can be seen in Figure 2A. This visualization describes the type of bond, bond distance, and the most important amino acid residues involved in the interaction of Ag85 B protein with β2 integrin can be seen in Figure 2B and Table III. The bonds are formed between Ag85 B and integrin β2 consist of 13 strong and stable hydrogen bonds. Of the 13 hydrogen bonds, only 2 bonds are on the side binding antigen receptor of the amino acid residues CYS-495 and GLN-494.

The binding interaction model number 6 between Ag85C protein and β2 integrin visualized using PyMOL software can be seen in Figure 3A. This visualization describes the type of bond, bond distance, and the most important amino acid residues involved in the interaction of Ag85 C protein with β2 integrin can be seen in Figure 3B and Table IV. The bonds formed between Ag85 C and integrin β2 consist of 21 strong and stable hydrogen bonds. The 21 hydrogen bonds, none are on the side binding antigen receptor of the amino acid residue.

Table III. Binding and amino acid residues of the Ag85 B *M. tuberculosis* protein to β2 integrin

Type of bond formed	Total number of bonds	Bond distance (Å)	Strength	Amino acid residues linked between ligand and receptor		Active amino acid residues between β2 integrin and native ligand NAG401
				Ag85 B amino acid	β2 integrin amino acid	
Hydrogen bond	13	2,5 Å	Strength	THR-215	PRO-530	CYS-535, VAL-526, CYS-495, GLY-509, GLN-510, GLN-494, ALA-395, LEU-420
		1,7 Å	Strength	ASN-231	ARG-541	
		2,0 Å	Strength	ASN-231	ARG-541	
		1,9 Å	Strength	SER-162	CYS-495	
		2,1 Å	Strength	SER-183	VAL-491	
		1,9 Å	Strength	SER-184	GLN-494	
		2,6 Å	Strength	SER-184	GLN-464	
		1,9 Å	Strength	SER-184	GLN-464	
		2,0 Å	Strength	ASP-185	GLN-462	
		2,2 Å	Strength	TYR-83	GLN-462	
		1,7 Å	Strength	SER-84	LYS-440	
		1,8 Å	Strength	TYR-83	LYS-440	
		2,0 Å	Strength	ASP-170	THR-499	

Description: THR, Threonine; PRO, Proline; ASN, Asparagine; ARG, Arginine; SER, Serin; CYS, Cysteine; VAL, Valine; GLN, Glutamine; ASP, Aspartic Acid; TYR, Tyrosine; LYS, Lisin (Source: 17)

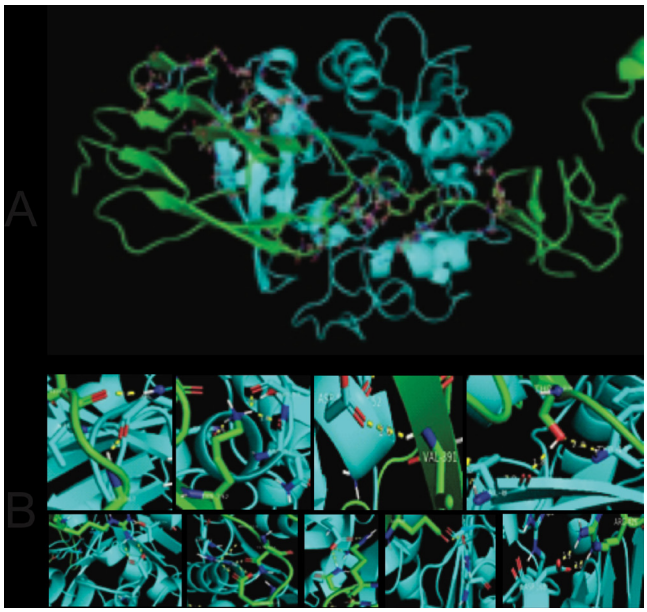

Figure 3: Interaction of amino acid residues between the *M. tuberculosis* Ag85 B protein and β2 integrin. ((A). Cartoon diagram of the binding interaction model 6 docking results between the *M. tuberculosis* Ag85 C protein and β2 Integrin (B). The bond distance (E) indicates the bond between two amino acid residues. The dashed yellow line represents the hydrogen bond distance between two amino acid residues. White – hydrogen, red – oxygen, and dark blue – nitrogen atoms. Ag85 C *M. tuberculosis* (cyan) and β2 integrin (green).

Table IV. Binding and amino acid residues of the *M. tuberculosis* Ag85 C protein to β2 integrin

Type of bond formed	Total number of bonds	Bond distance (Å)	Strength	Amino acid residues linked between ligand and receptor		Active amino acid residues between β2 integrin and native ligand NAG401
				Ag85 C amino acid	β2 integrin amino acid	
Hydrogen bond	21	2,0 Å	Strength	ARG-3	SER-365	CYS-535, VAL-526, CYS-495, GLY-509, GLN-510, GLN494, ALA-395, LEU-420
		2,1 Å	Strength	ARG-3	GLY-367	
		1,8 Å	Strength	GLU-57	ARG-371	
		1,9 Å	Strength	GLU-57	ARG-371	
		2,1 Å	Strength	GLU-57	GLN-390	
		2,0 Å	Strength	THR-53	LYS-392	
		1,8 Å	Strength	ASN-52	LYS-392	
		1,6 Å	Strength	ASP-50	LYS-392	
		2,6 Å	Strength	ASP-50	VAL-391	
		1,8 Å	Strength	VAL-8	THR-388	
		2,2 Å	Strength	TYR-10	THR-388	
		1,9 Å	Strength	THR-234	ARG-428	
		1,8 Å	Strength	GLU-155	ARG-428	
		2,0 Å	Strength	GLU-155	ARG-428	
		1,8 Å	Strength	ARG-41	GLN-422	
		1,7 Å	Strength	ARG-41	GLU-424	
		2,6 Å	Strength	ARG-41	PRO-421	
		2,0 Å	Strength	ARG-41	GLU-424	
		2,0 Å	Strength	ASP-168	ARG-426	
		1,9 Å	Strength	ASP-168	ARG-426	
		1,9 Å	Strength	GLN-73	GLN-418	

Description: ARG, Arginine; SER, Serin; GLY, Glysine; GLU, Glutamic Acid; GLN, Glutamine; THR, Threonine; LYS, Lysine; ASN, Asparagine; ASP, Aspartic Acid; VAL, Valine; TYR, Tyrosine; PRO, Proline (Source: 17).

DISCUSSION

Binding energy between Ag85 protein complex with β2 integrin

This research showed that the binding energy values for the nine bonds were negative. The molecular docking showed more negative binding energy values, indicating a stronger and more stable binding (18). The Ag85B protein and β2 integrin had the lowest binding energy value (-1055.0 kkal/mol) among the nine bonds. The Ag85B protein in the Ag85 protein complex is the most dominant protein secreted by M. tuberculosis. It is a potent immunoprotective antigen and can be the primary drug target. The β2 integrin is an integrin that is found freely in more than 40 ligands, including Fn, ICAM, and RAGE (19–21). A low binding energy value indicates that the ligand-protein complex formed is stable (22). The lower the binding energy value, the higher the affinity between the receptor and the ligand, the more spontaneous the ligand will form a complex with the receptor, and the higher the binding energy value, the lower the affinity between the receptor and the ligand (14). Therefore, the nine bonds were proven to show stable binding and have role in pathogenesis TB infection. The bond complex with the lowest binding energy value, which indicates that the bond formed is the most stable from the docking results, is then visualized using PyMOL software (22).

Model of binding interaction between Ag85 protein complex with β2 integrin

Visualization of bond interaction models can identify distances, amino acid residues, and types of bonds

formed in these interactions (23,24). The types of bonds formed in the results of this research are all hydrogen bonds. Hydrogen bonds affect protein activation. Hydrogen bonds occur when there is interaction between hydrogen atoms and electronegative atoms such as oxygen (O_2), nitrogen (N), and flour (F) (25). The binding energy value is the strength of the bond between the receptor and the ligand, which occurs intermolecularly through hydrogen bonds (22,26). The interaction between ligand and receptor upon hydrogen bonding indicates a stable bond (27).

The distance between the ligand and the molecule can impact bond interactions (23,28). The distance of the nine hydrogen bonds in this study ranged from 1.6 E to 2.8 E, showing strong bonds altogether. Bonds that have a value of less than 3E are strong. The stronger the bond interaction, the shorter the bond distance (23,28). Therefore, the results in this study all show strong hydrogen bonds and have potential as a secretory protein-based TB vaccine candidate.

The visualization results of amino acid residues show that the bond between Ag85 C and β2 integrin are not in the active site of the amino acid. Bonds that is not in the active site of an amino acid indicate that they cannot influence the action of a bond (29). In this case, Ag85 C, which binds to β2 integrin does not have a significant effect if used as TB vaccine antigens. These findings are in line with research conducted by Tufail Chaudhary and Hasnain (2016), which examined the alkylating agent S-303, which is unable to bind to the active site of CD-61, one of the primary antigens on platelets that aid in coagulation. They concluded that S-303 did not affect the CD-61 receptor, which is required for platelets to operate effectively despite having a negative binding energy (29). Therefore, the bond between proteins and the active site of amino acids is crucial to provide the desired working effect.

The visualization results of amino acid residues show that the bonds between Ag85 A, Ag85 B and β2 integrin, are on the active site of the amino acid. Active site prediction can also validate the role of active residues in ligand binding (30). β2 intergrin expression on dendrit cells, macrophages and monocytes. β2 integrins have three roles in immune regulation function: recruitment and migration, cellular interactions, and downstream cell signaling by mediating interactions between immune cells and pathogens. Interaction between Ag85 proteins with B2 integrin, enhance the adhesion and signaling of immune cells, thereby amplifying the immune response. This interaction might facilitate the recruitment and activation of T-cells and other immune cells at the site of infection (31).

CONCLUSION

This study proves that the complex Ag85 protein can bind to β2 integrin. Ag85B-β2 integrin bond exhibits the most stable and spontaneous binding, as indicated by lowest binding energy. This interaction occurs at the active site of the amino acid, enabling it to functionally enhance immune cell adhesion and signaling, it could amplify adaptive immune response.

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