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Molecular Docking Analysis of Lipoprotein Receptor Antigen I –Causing Endocarditis Interaction with Antibiotics and Immunoglobulins

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Author's contribution

Author BA designed the study, managed the literature searches, performed the analysis, wrote the protocol and wrote the manuscript.

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ABSTRACT

Bacterial endocarditis is a life-threatening infectious disease. In recent years, significant changes have occurred in risk factors, prophylaxis, common causative microorganisms, antibiotic resistance patterns of these organisms, diagnostic criteria, and antibiotic treatment of bacterial endocarditis. The viridans group of streptococci the most common cause of endocarditis, and its lipoprotein receptor antigen proteins (LraI) function as adhesins in several streptococci, as a virulence factor for endocarditis. The increasing trend of antibiotic resistance towards endocarditis, there is an immediate need to identify the mechanisms of molecular interactions of these virulence factors with common antibiotics and immunoglobulins. Thus, in this study, a group of five Streptococcal enzymes of LraI family (SsaB from *Streptococcus sanguinis*, ScaA from *S. gordonii*, PsaA from *S. pneumoniae*, FimA from *S. parasanguinis*, and ScbA from *S. cristatus*) were selected and considered as reactive sites. Three dimensional structure of the target receptor LraI family enzymes were docked with the antibiotic molecules using Hex 8.0.0 molecular docking method. The study found no potential affinity between the enzymes (receptors) and the antibiotics (ligands)

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during the molecular docking. However, a strong binding affinity towards IgM was observed with all the LraI family of five enzymes; hence, IgM was the most efficient antibody that could be used against bacterial endocarditis.

Keywords: Bacterial endocarditis; lrai family enzyme; antibiotics; antibodies; molecular docking.

1. INTRODUCTION

Streptococci in the mouth can cause a wide range of extra-oral diseases, most notably, infective endocarditis. This disease is a serious infection of the heart valves or endocardium, with complications that include congestive heart failure, aneurysm, and stroke [1]. Even though a range of antibiotic availability and improved medical facilities, in recent day's mortality rates of endocarditis ranging from 12 to 45% [2]. Bacterial endocarditis is occur when blood-borne bacteria colonize pre-existing cardiac "vegetations" composed predominantly of platelets and fibrin and formed in response to injury, as can occur with certain congenital cardiac conditions. Oral bacteria, especially oral streptococci [2], are a frequent cause of endocarditis. There are many potential virulence factors of enzymes released by various oral streptococci such as ScbA, ScaA, FimA, PsaA, SsaB and EfaA from *S. cristatus, S. gordonii, S. parasanguis, S. pneumoniae, S. sanguis* and *Enterococcusfaecalis* respectively. These enzymes are highly conserved cell surface receptors known as LraI (lipoprotein receptor antigen I protein) family [3,4] Prevention of endocarditis is highly essential, as the disease is always fatal if untreated. Concerning the treatment of bacterial endocarditis, the choice of antibiotic therapy is determined by the type of bacterial isolates and its susceptibility patterns. Additionally, other contributing factors, such as the type of cardiac valves, either native or prosthetic, health conditions of patients and drug allergies should be considered. Unfortunately, in recent years, the treatment of endocarditis has become more complicated because of the development of antibiotic resistance in organisms. Multi-drug resistant enterococci have shown resistance to multiple antibiotics that are currently available to treat endocarditis, including vancomycin and teicoplanin [5-7].

Thus, there is an essential need to analyze the molecular interactions of virulence factors and common antibiotics used for treating meningitis. Search for effective preventive medicines and defensive immune mechanisms has become the need of the hour, which has also become the great concern and anxiety amongst the physicians that made them to search for an alternative to the chemical control methods.

The aim of the present study was to illustrate the application of computational docking to the study of antibiotics-antigen interactions, and then highlight the strengths and weaknesses of the approach by predicting the binding of different immunoglobulins to the virulence protein LraI enzymes of bacterial endocarditis.

2. MATERIALS AND METHODS

2.1 Reactive Site

Proteins related to the LraI (for "lipoprotein receptor antigen") family function as adhesins in several streptococci species, which is a vital virulence factor causing endocarditis. Therefore, it was considered as reactive site. The structures of LraI enzymes and immunoglobulins such as IgG, IgA and IgM were retrieved from the protein data bank (http://www.rcsb.org/) [8].

2.2 Preparation of Ligands

The most commonly available antibiotics that are used to treat for bacterial endocarditis were retrieved from Chem Spiderdatabase [http://www.chemspider.com/] and were considered as ligands. These secondary structures were later converted into 3-D structures using Swiss Pdb viewer [http:// www.spdbv.vital-it.ch/] [9,10].

2.3 Molecular Docking Analysis

The molecular docking between receptor and ligand was carried out by Hex8.0.0 docking program [http://www.hex.loria.fr/dist50/] [11]. It was performed by adjusting appropriate parameters such as twist range-360, receptor range-180, ligand range-180, FFT mode-3D fast lite, grid dimension-0.6 and distance range-40. The obtained scores of binding energy (E values) was tabulated and analyzed.

3. RESULTS AND DISCUSSION

The treatment of endocarditis has become more complicated because of the antibiotic resistance, and the development of allergic reactions among the patients due to indiscriminate use of antibiotics. Since *Streptococcus* species are becoming resistant to antibiotics and capable of acquiring multiple drug resistance, the traditional practice of chemotherapy proved futile, and hence search for new alternative therapeutic procedure becomes the need of the hour [12,13]. In this context, a variety of bioinformatics tools and methods could be successfully used to identify the effective drugs. One of such tools and techniques is docking of drug molecules with receptors. The energy value obtained through docking is used as a criterion for measuring the effectiveness of the drugs molecules, which are called lead molecules. In this study access the molecular interactions between a virulent factor of bacterial endocarditis with available commonly antibiotics and human immunoglobulins [14,15]. The lead molecules are those with maximum interaction having high negative e-value [16].

In the present study, enzymes of LraI family such as SsaB, ScaA, PsaA, FimA and ScbA were targetedas receptors. Antibiotics such as penicillin, vancomycin, streptomycin and erythromycin, and antibodies including IgA, IgG and IgM were used as ligands. The 3D structures of LraI family enzymes were retrieved from Swiss Prot and protein data bank. The volume of the enzymes of LraI family was ranging from 26985 to 28158 in $Å^3$. Among them, the enzymes such as PsaA, FimA and SsaB, formed by 309 amino acids, which were larger and determined as 28116, 28120 and 28158 $Å^3$ respectively. The polypeptide chains of ScaA and ScbA were formed by 310 amino acids each and the volumes of these enzymes were 27921 and 27647 $Å^3$ respectively. The number of polypeptide strands, helices, turns and H-Bonds was also noticed and presented in Table 1 and Fig. 1.

In each enzyme, ten binding sites were identified on the surface as well as on the interior of the enzyme molecule in different volumes. These binding sites were recognized by the ligand molecules. Commonly, the larger binding site is the major active site that is recognized by the ligand molecules. The occurrence of molecular docking between the ligands and the recognized active binding sites of the enzymes was observed. The volume of the binding sites varied from enzyme to enzyme among the LraI family and it was ranging from 81 to 216 $Å^3$. Notably, the volumes of the active (larger) binding sites of LraI family enzymes were 192, 193, 189, 213 and 216 $Å^3$ in ScaA, PsaA, FimA, ScbA and SsaB respectively (Table 2, Fig. 2).

Table 1. Characteristic features of 3D protein structures of LraI family of enzymes

Structure of enzymes	H-bonds	Helices	Strands	Turns	Enzyme volume ($Å^3$)
FimA	192	14	16	26	28120
SsaB	192	14	16	26	28158
ScaA	188	13	16	26	27921
PsaA	192	14	16	25	28116
ScbA	188	13	16	26	27647

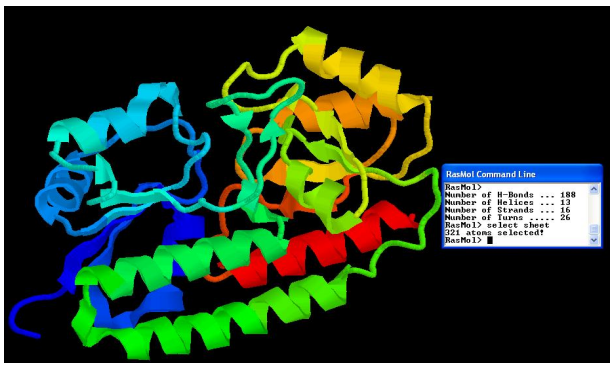

Fig. 1. Three dimensional protein structures of ScaA

Table 2. Volume of binding sites in LraI family of enzymes

Site Number	Binding site volumes in Å^3				
	ScaA	PsaA	FimA	ScbA	SsaB
1	192	193	141	213	189
2	157	139	184	176	155
3	163	160	189	162	216
4	167	155	153	144	160
5	152	130	133	126	160
6	101	155	122	123	125
7	117	117	122	122	120
8	99	118	157	129	104
9	124	111	119	126	85
10	93	94	129	125	81

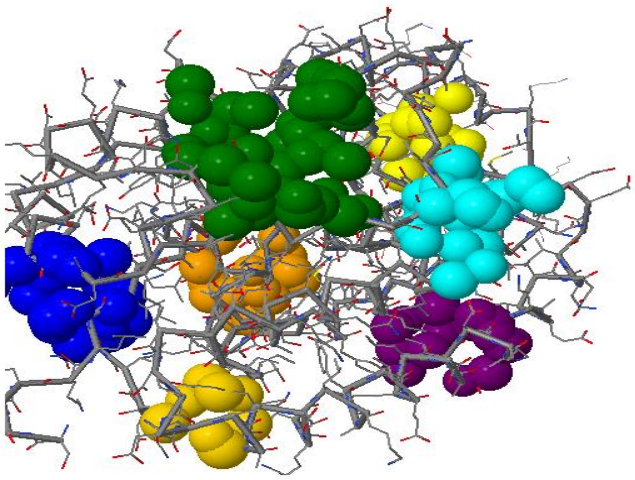

Fig. 2. The binding sites in ScaA (Major active sites are green in color)

Molecular docking was performed between the enzymes, the receptors and ligand molecules (Figs.3 A-D and 4. A-C). The target LraI family of enzymes (antigens) and ligands were geometrically optimized. All the ligand molecules were docked against the active sites of the target antigen using Hex 8.0 software. The docking results are represented in the form of e-negative values (Table 3). In the docking studies, higher negative e-values represent a high binding affinity between the receptor and ligand molecules, indicating the higher efficiency of the antibiotics or the immunoglobulins.

ScaA of *S. gordonii,* on docking with drugs such as penicillin G, streptomycin, vancomycin and erythromycin produced energy values such as -51.51, -67.48, -177.86 and -179.93KJ/mol respectively (Fig. 5. A-D). Similarly, the other enzymes of the LraI family were also docked with all the four antibiotics and the e-values obtained from the docking were ranging from -53.59 to -193.35 KJ/mol. The results showed that all the antibiotics with target antigens produced low negative e-value when compared to immunoglobulins (Table 3). Thus, it is clear that the antibiotics were not able to interact with any of the available binding sites of the LraI family enzymes effectively. Based on the molecular interactions by docking studies indicated that antibiotics used for endocarditis treatment were not able to inhibit the activity of the LraI enzymes effectively.

Regarding molecular docking against immunoglobulin, the ScaA with immunoglobulins IgA, IgM and IgG produced energy values such as -393.08, -774.14 and -627.83 KJ/mol respectively. Among the three immunoglobulins IgM showed a higher negative energy value of -774.14 than that of IgA and IgG (Table 3, Fig.6 A-C). Similarly, all the immunoglobulins were also docked with other five enzymes of LraI family. The e-values obtained through the above

docking were -378.31 to -774.14, which were much higher than that of the antibiotics. Among the three immunoglobulins, IgM showed higher negative e-values with all the enzymes of LraI family. The e-values obtained through the molecular interactions between IgM and the enzymes of the LraI family were -732.19,-717.34,-684.30,-708.55 KJ/mol and respectively with SsaB, PsaA, FimA, and ScbA indicating IgM as the predominant immunoglobulin able to control the early activity of bacterial enzymes causing endocarditis (Table 3).

Therefore, the above study indicates that the antibiotics were not effective in inhibiting the activity of the enzymes causing bacterial endocarditis. Interestingly, it is very much evident that there is no effective preventive medicine and defensive immune mechanisms available at present. Hence, the evolution of new preventive strategies to overcome the disease problem is warranted. In this context, the alternative approach, such as the effective induction of the local immune system, is expected to ensure the prevention and control of bacterial endocarditis. Many researchers investigated the significance of essential enzymes and their specific structures in microbes that has been evolved as a target for the drug development. Priyadarshini et al (2013) found that 3-oxoacyl-(acyl-carrier-protein) synthase III (FabH) as an attractive drug model against pathogens that causing infective endocarditis [17]. Lu et al and Zhang et al utilized

Table 3. E-values obtained from the docking studies between LraI enzymes and ligand molecules (antibiotics and immunoglobulins)

Organism name	Enzymes	Name of the Ligands	E-value (KJ/mol)
S. gordonii	ScaA	IgA	-393.08
		IgM	**-774.14***
		IgG heavy chain V-II region	-627.83
		Penicillin G	-51.51
		Streptomycin	-67.48
		Vancomycin	-177.86
		Erythromycin	-179.93
S. sanguinis	SsaB	IgA	-381.96
		IgM	-**732.19***
		IgG heavy chain V-II region	-620.15
		Penicillin G	-56.34
		Streptomycin	-73.48
		Vancomycin	-167.99
		Erythromycin	-168.05
S. pneumoniae	PsaA	IgA	-378.31
		IgM	**-717.34***
		IgG heavy chain V-II region	-574.39
		Penicillin G	-53.59
		Streptomycin	-75.37
		Vancomycin	-145.33
		Erythromycin	-188.46
S. parasanguis	FimA	IgA	-403.06
		IgM	**-684.30***
		IgG heavy chain V-II region	-598.36
		Penicillin G	-54.93
		Streptomycin	-77.21
		Vancomycin	-160.84
		Erythromycin	-191.60
S.crispatus	ScbA	IgA	-400.01
		IgM	**-708.55***
		IgG heavy chain V-II region	-611.19
		Penicillin G	-56.34
		Streptomycin	-77.06
		Vancomycin	-164.08
		Erythromycin	-174.71

** Selected immunoglobulin based on the e-value*

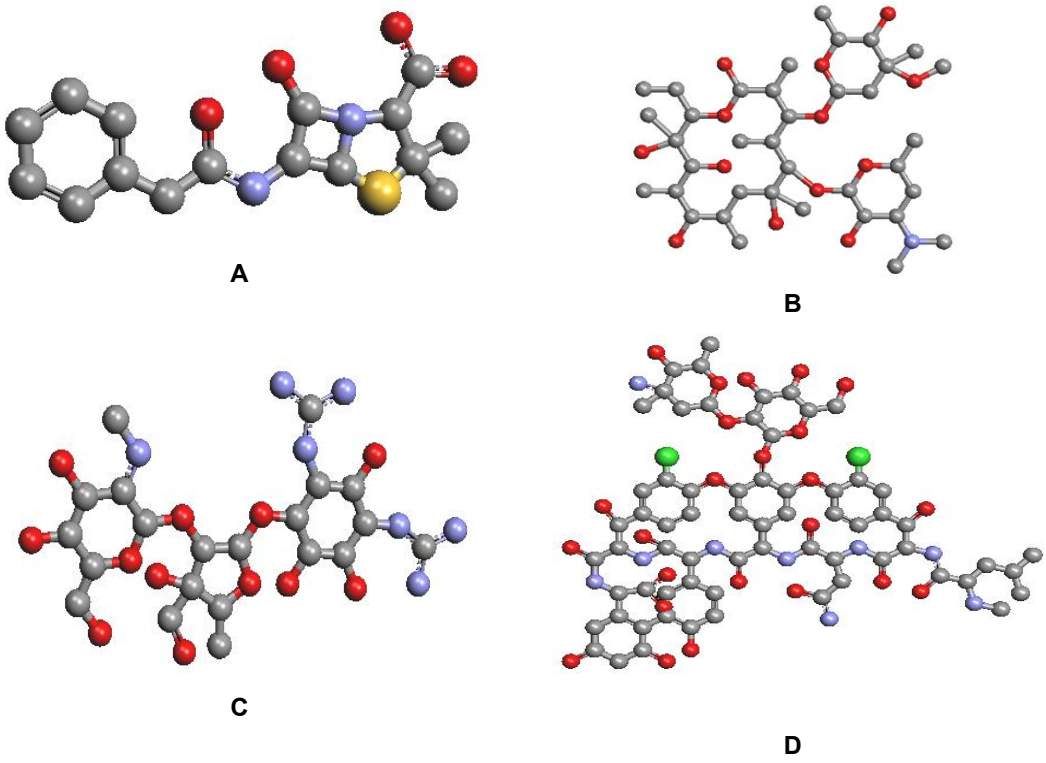

Fig. 3. Structure of antibiotics of ligands (A - Penicillin G; B - Erythromycin; C - Streptomycin; D - Vancomycin)

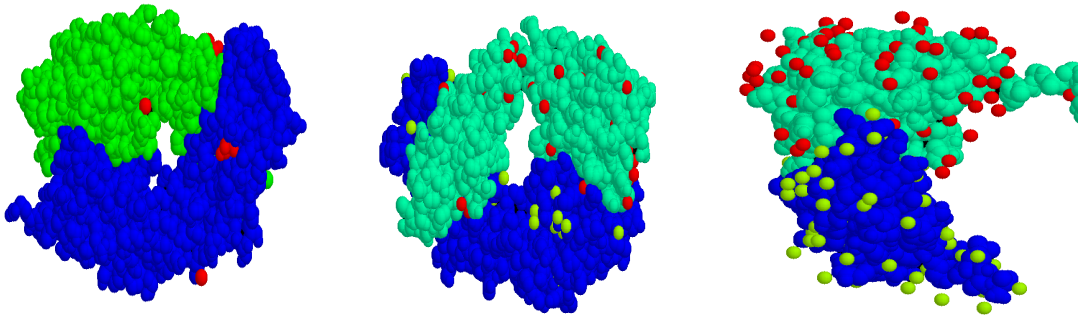

Fig. 4. Structure of immunoglobulins of ligands (Blue colour indicates heavy chain and green colour indicates light chains)

these specific features to develop drug targets especially FabH inhibitors in *Mycobacterium tuberculosis* [18] and in *Escherichia coli* [19].

In the present study, the alternative approach as an assessment of binding affinity towards IgM was observed with all the LraI family of five enzymes. The analysis indicated the potentiality of IgM based strategies of drug target against microbes that causes bacterial endocarditis. Neves Forte et al investigated the immune response in the peripheral blood from the IE patients with infective endocarditis. They found that there was a significant increase of T and B lymphocytes, CD4+ and CD8+ cells, IgM, IgG, and C4 complement component during active infection [20]. Hence, the results clearly indicate that the levels of both IgG and IgM in the patients

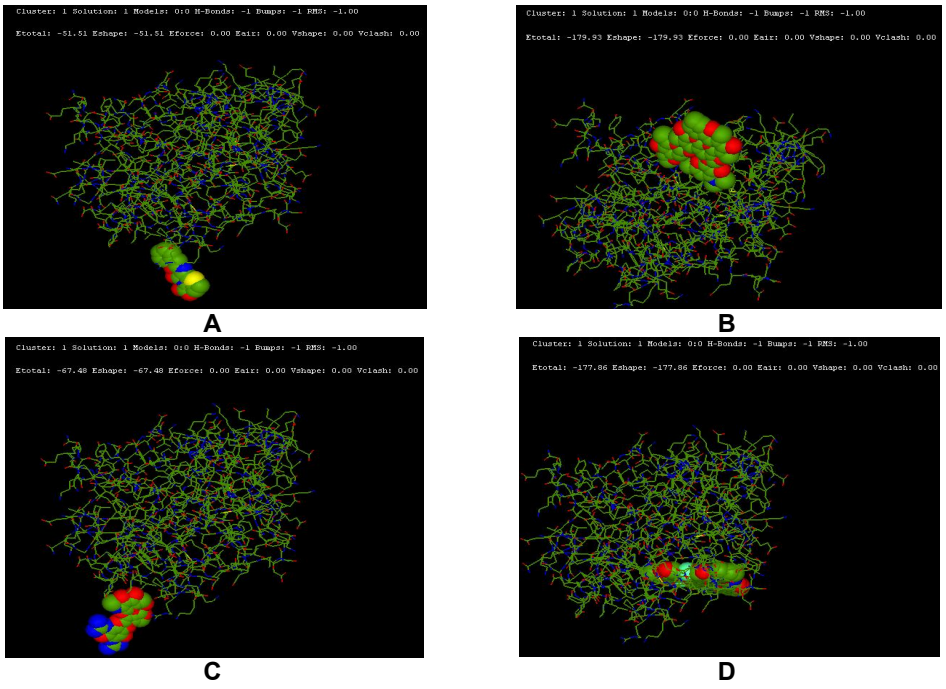

Fig. 5. Molecular docking of ScaA enzyme with antibiotics of penicillin G (A), erythromycin (B), streptomycin (C) and vancomycin (D) (Green balls indicate ligands, green line complex of structure indicates receptors)

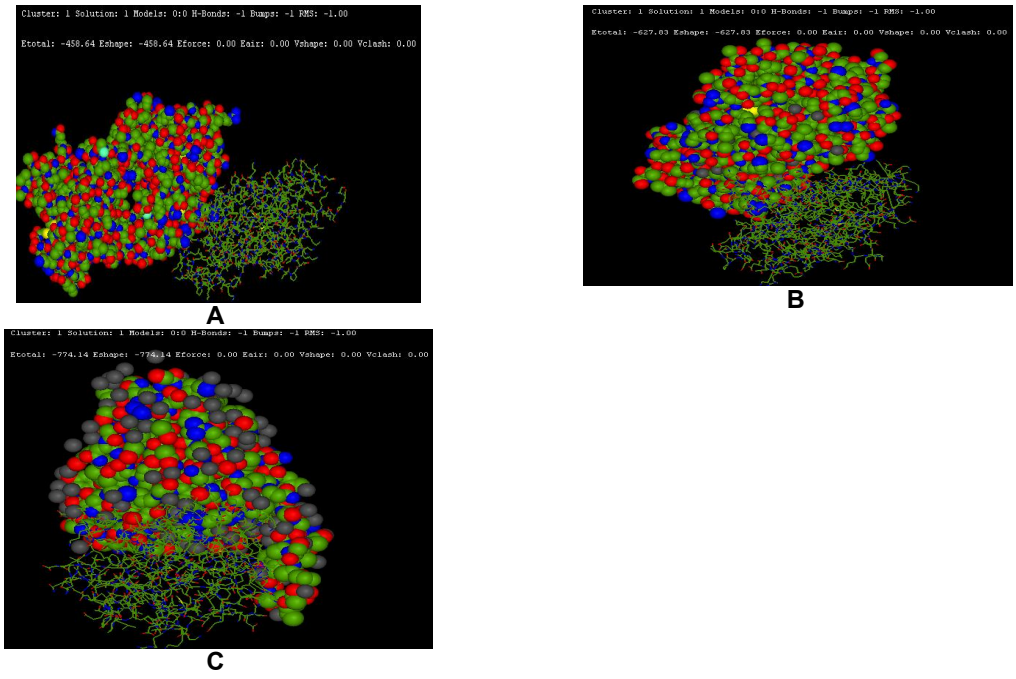

Fig. 6. Molecular docking of ScaA enzyme (green lines) with immunoglobulins (green, blue, black balls) complex (A-IgA; B-IgG; C-IgM)

with bacterial endocarditis could be in response to the elevated levels of antigens in the circulating immune complexes. Similarly, it has also been reported that there was the occurrence of heavy intra valvular deposits of IgG as well as bacterial antigen in the case of bacterial endocarditis caused by *S. viridans* [21].

Holland and his associates found that there was more focal interstitial IgM and deposits, also large number of immune reactants and constituents of immune complexes present in valves and vegetations of patients with bacterial endocarditis [22]. These findings categorically state that there was frequent increase in the level of the IgM in the sera of patients with prolonged duration of bacterial endocarditis. Interestingly, sequential studies also revealed that there was IgM in the sera of patients infected with endocarditis and reported a strong IgM response to EfaA antigen in patients suffering from enterococcal endocarditis. Later it was also found that there were a, number of protein antigens and IgM in *E. faecalis* infected endocarditis [23].

In the present study also revealed that the molecular docking of antigens with antibody IgM showed higher negative energy value with all the enzymes of the LraI family than that of IgA and IgG, and hence, IgM has been considered as an effective immunoglobulin because of its maximum interaction having higher negative e-values.

4. CONCLUSION

The docking analysis showed that the test antibiotics used to treat bacterial endocarditis, including streptomycin, erythromycin, Penicillin G were not effectively bound with LraI family of enzymes. The study also exhibited that IgM based drug targets could be a capable drug candidature by the In-Silico method, and the same is recommended to be considered while modeling a new drug against infectious bacterial endocarditis. These data could be of interest to the researchers in conducting further studies as to evaluate drug targets.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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