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Computational Repurposing of Certain Monoclonal Antibodies for the Treatment of Systemic Lupus Erythematosus

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Abstract

Objective: More than 3 million individuals globally suffer from systemic lupus erythematosus (SLE) with no radical therapy for such a multi-organ disease. The present *in silico* study explores the virtual repurposing of certain monoclonal antibodies (mAb) against the emerging target toll-like receptor 7 (TLR-7).

Materials and Methods: The 3D structure of TLR-7 and the shortlisted mAb were retrieved from Alphafold and Thera-SabDab datasets, which were then subjected to docking by pyDockWEB and HDOCK webservers. Molecular dynamics (MD) simulations and MM/GBSA were also predicted for the best docked complex.

Results: Bevacizumab was the best potential antagonist mAb of human TLR-7 in terms of protein docking. MD simulations unveiled the stability and the flexibility of the docked complex and MM/GBSA predicted the hotspot residues of the TLR-7-Bevacizumab.

Conclusion: Bevacizumab can be deemed as potential repurposed mAb for treating SLE *in silico*, which needs experimental validation.

Keywords: Systemic lupus erythematosus, autoimmune disease, mAb, docking, MD simulations

Introduction

Systemic lupus erythematosus (SLE) is a multifactorial disease affecting many human body systems leading, if untreated, to death (1). The global epidemiology of SLE is estimated to be nearly 3.41 million, with the female gender being the most afflicted (9 females for every male) (2). Adults are 1.42-fold susceptible to SLE than other overall population (3). The severity of the disease varies considerably from mild and moderate to severe and it has been reported to be dependent on ethnic demographic background and Latin Americans who are at higher risk as well as Africans (4). Life expectancy has been shown to be markedly lower in SLE according to the degree of multi-organ damage. In contrast, about 80-90% of SLE patients seeking firm follow-up have near normal age (5). Although the disease is classified as an autoimmune disease, the major cause is still unknown (6). The well-known events in SLE are the presence of autoantibodies in the circulation against DNA and cytosol components secreted by plasma cells (7). Dysregulated cytokines also play a significant part in SLE pathology (8). Both of them are responsible for the multi-organ (brain, kidneys, joints and lungs) damage and are generated from the same ancestor, B lymphocytes (9). The underlying mechanism through which SLE develops is thought to be ongoing exposure and presenting of self-antigens to the immune cells, possibly from an excessive apoptotic cell load, that commences a feed-forward loop between innate and adaptive immune systems (10). This in turn continuously instigates the production of autoantibodies and immune complexes, autoreactive T-cells and B-cells, complement activation, and cytokine release, which ultimately results in widespread tissues damage, manifesting as the clinical image of SLE pathogenesis (11).

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As having demonstrated its key involvement in SLE pathogenesis, B cells are the main target for immunotherapy using the specific biopharmaceuticals monoclonal antibodies (mAb) (12). B-cell activating factor is an important cytokine that activates and differentiates B-cells and, thus, is a significant druggable target (13). It was targeted by several mAbs such as Belimumab, Blisibimod and Tabalumab. However, only Belimumab gained US Food and Drug Administration (FDA)-approval. Besides, Rituximab (FDA-approved), Obinutuzumab, Ofatumumab, Epratuzumab and Ocrelizumab were designed to block CD20 from binding to its cognate ligand and, hence, mediate transient B-cell depletion (14). Albeit the testing of various array of mAb as an innovative, selective intervention toward SLE, they suffer from major drawbacks including low potency and serious side effects (15). In addition, interferon receptor blockade was shown to pose positive influence for SLE therapy (16). Indeed, Anifrolumab gained FDA-approval in 2021 (17).

More recently, toll-like receptor 7 (TLR-7) proved itself as unprecedented key druggable target to treat SLE given the fact that it has earlier role in the implication of SLE (18). In reality, TLR-7 has gained enormous attention as it senses double-stranded DNA, which is believed to be the first signal responsible for the recognition of self-DNA as non-self (19). Experimental evidence proved that TLR-7 gain-of-function genetic variants resulted in SLE development (20). Therefore, TLR-7-interfering agents are racing to gain FDA-approval (21-23). Herein, virtual repurposing of mAb against the emerging SLE target TLR-7 is explored by bioinformatics tools.

Materials and Methods

The outlined workflow of the current *in silico* study is summarized in Figure 1.

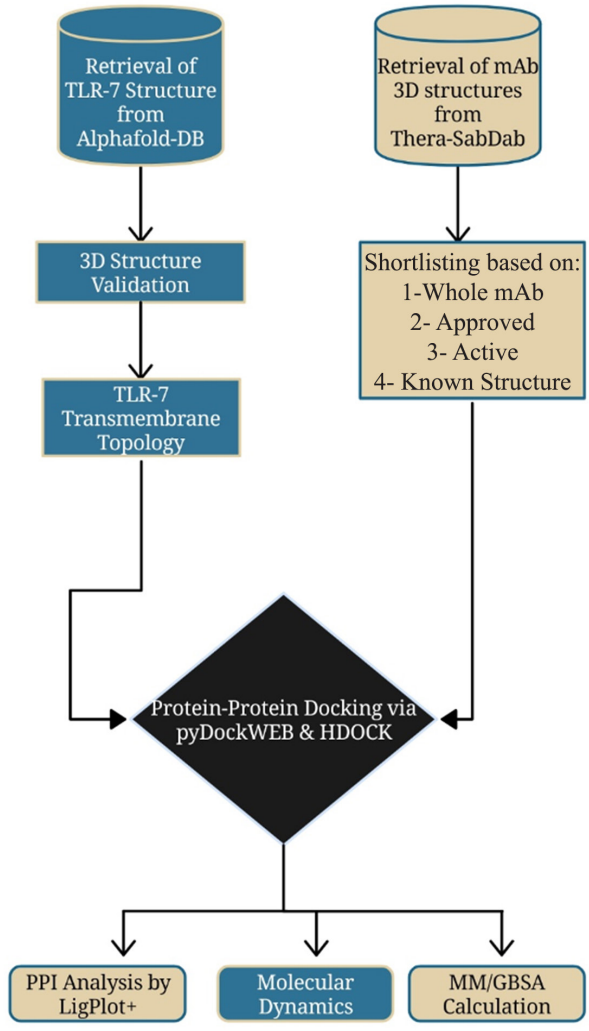

Figure 1. Flowchart summarizing the methodology followed in the present study.

Retrieval of Protein Structures

The receptor structure of human TLR-7 was retrieved from Alphafold database (ID# Q9NYK1) (24), which was checked for its quality via SWISSMODEL platform (25). On the flip side, Thera-SabDab database (26) was utilized for the retrieval of mAb 3D structures. The selection of mAbs was based on four inclusion criteria: (i) whole mAb types, (ii) being approved by FDA, (iii) being still in the active manufacturing status and (iv) having their 3D architecture deposited in protein data bank. Otherwise, human-non-specific mAb, SARS-CoV-2 specific mAb, mAb with huge structure and mAb with bad structures resolution were all excluded. This yielded only 35 mAbs which were selected for further consideration.

Transmembrane Topology

The retrieved and validated structure of TLR-7 was subjected to transmembrane topology prediction through OREMPRO tool (27). This was purposed to identify and excise only the extracellular domain responsible for binding ligands.

Molecular Docking

Protein-protein docking analysis was performed via pyDockWEB (28) and validated using HDOCK servers (29). pyDockWEB server gives detailed energy profile such as VdW, desolvation and electrostatic forces of the docked complex. Further analysis of the best docked TLR-7-mAb complex was done using LigPlot+ program (30) through antibody module.

Molecular Dynamics and MM/GBSA Valculation

The best docked complex was subjected to molecular dynamics (MD) simulations so as to investigate the stability, flexibility and correlation of residues and the whole complex upon motion via iMODS online tool (31).

This was followed by the in-depth identification of hotspot residues from TLR-7 as well as the mAb revealed by molecular mechanics-generalized born surface area (MM/GBSA) calculation as predicted by HawkDock web portal (32).

Results

Homology Modelling

The predicted model from alphafold database was assessed by SWISS-MODEL platform. The model had a MolProbity value of 1.34, clash score 0.99, Ramachandran favored regions 93.89% and QMEANDisCo Global 0.76, indicating the significantly good quality of the modelled architecture (Figure 2).

Topology Predictions

According to OREMPRO output, TLR-7 has a signal peptide (first 27 residues), a single transmembrane domain (840-868) with a hydrophobic thickness of 30.0 Å and a tilt angle of 40.6 as depicted in Figure 3. Hence, only the extracellular domain, i.e. residues 28-823, was selected for further analysis since it is the domain where binding site is located to be docked against the mAb.

Docking

Table 1 elucidates the docking scores of the examined mAb using pyDockWEB and HDOCK servers.

The docking scores of the two servers elected Bevacizumab as the best potential mAb to antagonizes human TLR-7 since it had total energy of -53.004 kcal/mol in pyDockWEB and -326.77 kcal/mol in HDOCK. This total energy is accounted for -5.792 kcal/mol electrostatics, -46.019 desolvation energy and -11.927 kcal/mol VdW interactions. Besides, tralokinumab and certolizumab are the less potential candidate antagonists for TLR-7 given that the total energy was -47.267 and -50.641 kcal/mol, respectively. Correlation coefficient (R) equals 0.5061 between pyDockWEB and HDOCK servers. This means that there is a moderate direct relationship between pyDockWEB and HDOCK docking scores.

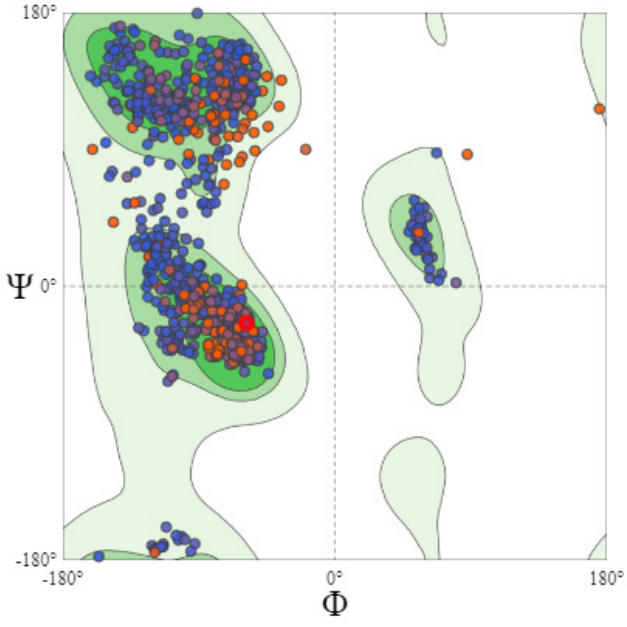

Figure 2. Ramachandran plot of human TLR-7 retrieved from Alphafold database.
TLR-7: Target toll-like receptor 7

Protein-protein interactions were revealed using LigPlot+ program. This reported 7 H-bonds formed between TLR-7 and Bevacizumab. Three of the H-bonds of the mAb were from the heavy chain whereas the other two were from light chain. Furthermore, many residues were involved in VdW interactions between the receptor and mAb as illustrated in Figure 4. To further explore the hotspot residues that contributed mostly to the binding energy, MM/GBSA calculation was performed using HawkDock webserver. The binding free energy of receptor-mAb complex was -47.74 kcal/mol. Three Phe were the most active hotspot residues from the receptor side, namely Phe-444, Phe-507 and Phe-506 with binding free energy -5.44, -4.55 and -3.22 kcal/mole (Table 2). However, Phe 506 and Phe 507 in LigPlot+ of the docked complex constituted VdW attraction which can be attributed to the minimization step that occurred during MM/GBSA calculation accompanied by conformational changes that put such residues in the face of formation of H-bonds instead of VdW. The same interpretation can be inferred with respect to mAb hotspot residues (Figure 5).

MD Simulations

I scrutinized the conformational changes and their implications on the stability, flexibility as well as the variance and correlation of the interacting complex residues. It is clear that there was slight but significant difference between the conformers of TLR-7-mAb complex as evident from the first (Figure 6A) and last (Figure 6B) conformer directions upon molecular motion. This is emphasized by the low deformability level of the complex (Figure 6C) indicating the relatively compact architecture and thus high stability. The low mobility (B factor) described the strong association between the interacting protein complexes (Figure 6D). The eigen value is another important parameter that explains the stability of the protein complex in terms of deformation energy such that low eigen value means higher stability which is the scenario we got in the docked proteins (Figure 6F). Furthermore, the flexibility of TLR-7-mAb complex was significantly good as observed by the variance percentage in Figure 6E. Moreover, harmonic cumulative motion was also observed for the interacting protein complex as mirrored by the correlated Cα-atoms (Figure 6G-H) between the receptor and mAb.

Table 1. Docking scores of all selected mAbs and TLR-7

No.	mAb	pyDockWEB				HDOCK score
		Electrostatics	Desolvation	VdW	Total	
1	Adalimumab	-15.591	-27.771	37.933	-39.569	-278.25
2	Alemtuzumab	-16.697	-12.72	29.255	-26.492	-263.19
3	Anifrolumab	-11.114	-21.546	62.369	-26.424	-256.36
4	Ansuvimab	-16.144	-19.604	53.863	-30.362	-281.87
5	Avelumab	-13.117	-26.157	22.134	-37.061	-250.73
6	Belimumab	-14.25	-24.289	53.508	-33.188	-260.68
7	Bevacizumab	-5.792	-46.019	-11.927	-53.004	-326.77
8	Bintrafusp	-14.25	-24.289	53.508	-33.188	-250.73
9	Canakinumab	-16.716	-23.151	2.386	-39.628	-265.5
10	Certolizumab	-14.895	-40.828	84.559	-47.267	-304.02
11	Cetuximab	-12.335	-24.439	58.077	-30.967	-298.79
12	Daclizumab	-22.263	-12.109	-20.975	-36.469	-271.59
13	Daratumumab	-12.298	-33.367	37.201	-41.945	-290.42
14	Dupilumab	-12.983	-19.564	5.379	-32.009	-263.66
15	Durvalumab	-8.571	-37.572	50.898	-41.054	-266.08
16	Guselkumab	-12.98	-24.801	66.168	-31.165	-263.5
17	Ipilimumab	-12.491	-34.141	73.318	-39.3	-269.65
18	Ixekizumab	-12.574	-16.499	0.001	-29.074	-280.88
19	Loncastuximab	-8.23	-20.385	-16.743	-30.29	-252.04
20	Natalizumab	-18.358	-10.234	11.99	-27.392	-253.85
21	Necitumumab	-5.985	-34.714	27.668	-37.932	-286.6
22	Nimotuzumab	-12.27	-28.293	48.299	-35.733	-269.21
23	Nivolumab	-10.568	-21.392	37.234	-28.237	-273.17
24	Ofatumumab	-6.425	-34.772	35.068	-37.69	-279.34
25	Olokizumab	-13.553	-18.777	9.365	-31.393	-300.43
26	Panitumumab	-26.26	-15.341	48.575	-36.744	-299.33
27	Pertuzumab	-15.12	-27.319	21.992	-40.24	-302.47
28	Ramucirumab	-15.257	-15.717	16.182	-29.355	-276.64
29	Rituximab	-30.436	-10.801	101.88	-31.049	-270.9
30	Secukinumab	-7.49	-30.431	25.955	-35.326	-250.91
31	Serplulimab	-3.372	-28.938	8.932	-31.416	-292.85
32	Tezepelumab	-14.007	-26.602	28.056	-37.804	-302.02
33	Tislelizumab	-23.679	-16.249	30.266	-36.901	-304.53
34	Tralokinumab	-13.387	-42.471	52.168	-50.641	-286.31
35	Ustekinumab	-12.895	-32.238	50.161	-40.117	-277.27

TLR-7: Target toll-like receptor 7

Discussion

A set of 35 mAbs were screened for their capability to block human TLR-7 by protein docking servers (pyDockWEB and HDOCK) after cropping only the extracellular domain of the receptor. Bevacizumab was the lead potential mAb that could antagonize TLR-7 action as shown by its highest docking scores in the two servers. Moreover, MM/GBSA free energy of binding of -47.74 kcal/mol in addition to the 7 H-bonds formed between the TLR-7 and the mAb, which confirms the binding strength. MD simulations demonstrated the stability, flexibility, avidity and correlated motion of the docked complex as

reflected by deformability, mobility (B-factor), eigen value and covariance map (Figure 6) (31,33).

SLE is a chronic multi-organ disease of an autoimmune origin that is associated with high rate of morbidity and mortality (34). The exact etiology remains to be discovered but genomic (inherited) and exposomic (environmental) factors merge at the epigenomic level to drive the pathogenesis of the disease (35). N-acetyltransferase 2 genotype dramatically raises the predisposition to SLE (36). On the other hand, diet poor with polyunsaturated fatty acids (both ω-3 as well as ω-6), cigarette smoking, caffeine-rich beverages and UV-radiation exposure are some external factors (36). It was reported recently that TLR-7 together with tumour-necrosis factor-α (TNF-α) were associated with a potential female-specific mechanism in the pathogenesis of autoimmune-induced hypertension. It was found that TLR-7 and its downstream proinflammatory cytokine TNF-α levels were much higher in female compared to male, a fact accounting for the higher SLE prevalence in female (19). Given that there is no FDA-approved mAb targeting TLR-7 to date, virtual repurposing of available mAb for the treatment of SLE was sought in the current work.

The utilization of computational screening and design strategies, coupled with mutational and binding analyses of mAb, is currently experiencing a notable upward trajectory within the contemporary realm of immunoinformatics. This approach is gaining prominence for repurposing mAbs to address novel disorders. In this context, Depetris et al. (37) theoretically designed KD035, a mAb blocking vascular endothelial growth factor receptor 2 and validated the selectivity based upon mutational and binding analysis. Wolf Pérez et al. (38) designed 17 variants of a humanized mAb (IgG4) for improving the solubility of the precursor mAb using CamSol tool. The enhanced *in silico* variants were validated by *in vitro* setting, which provided acceptable findings. Similarly, a testing about 8 mAb manufactured for COVID-19 therapy and the design of chimeric mAb by conjugating the CDRH3 of regdanivimab with sotrovimab scaffold in order to combat the variants that could get escaped from the mAb neutralization (33).

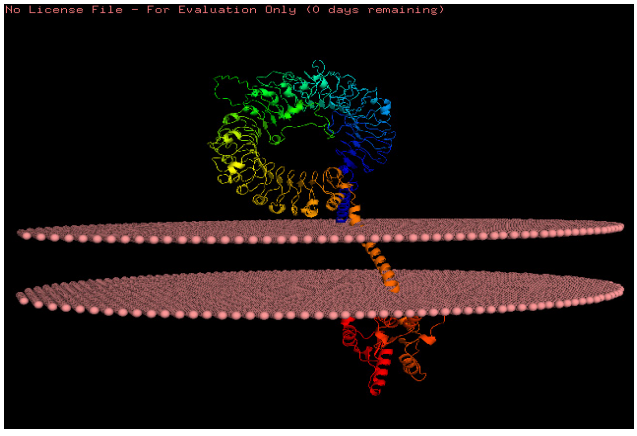

Figure 3. Transmembrane topology of TLR-7 as predicted by OREMPRO tool.
TLR-7: Target toll-like receptor 7

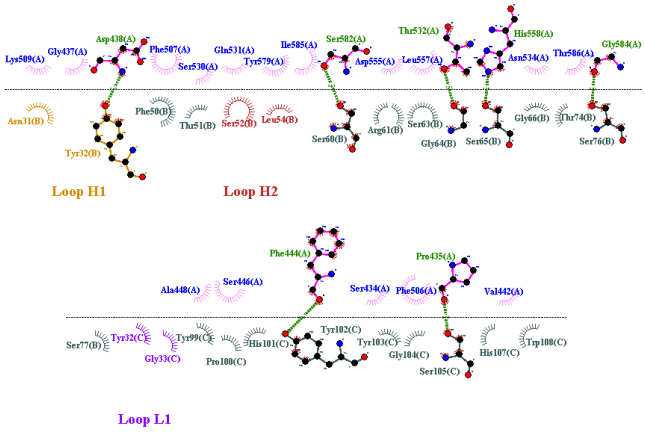

Figure 4. Protein-protein interactions of TLR-7 and Devacizumab. Heavy chain loop 1 in orange, loop 2 in firebrick, light chain loop 1 in purple while other antibody residues are in dim grey.
TLR-7: Target toll-like receptor 7

Study Limitations

The limitation of this study is that the binding potential of bevacizumab was based on the docking, MD simulation and MM-GBSA output (theoretical experimentation), which deserves *in vitro* and *in vivo* experiments.

Table 2. Obtained MM/GBSA of the docked complex between TLR-7 and Bevacizumab

TLR-7		Bevacizumab	
Residue	Binding free energy	Residue	Binding Free Energy
A-Phe-444	-5.44	B-Ser-76	-3.25
A-Phe-507	-4.55	B-Phe-50	-2.87
A-Phe-506	-3.22	B-Tyr-32	-2.49
A-Ile-585	-2.73	C-Ser-105	-2.51
A-Val-442	-2.23	C-Trp-108	-2.28

TLR-7: Target toll-like receptor 7

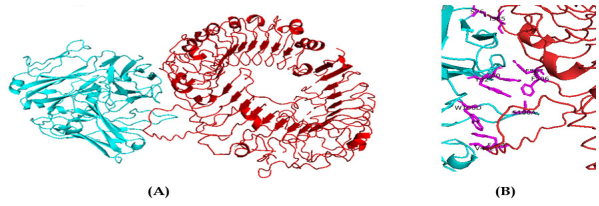

Figure 5. Docked complex between TLR-7 shown in red and Bevacizumab shown in cyan (A). The hotspot residues were also depicted (B).
TLR-7: Target toll-like receptor 7

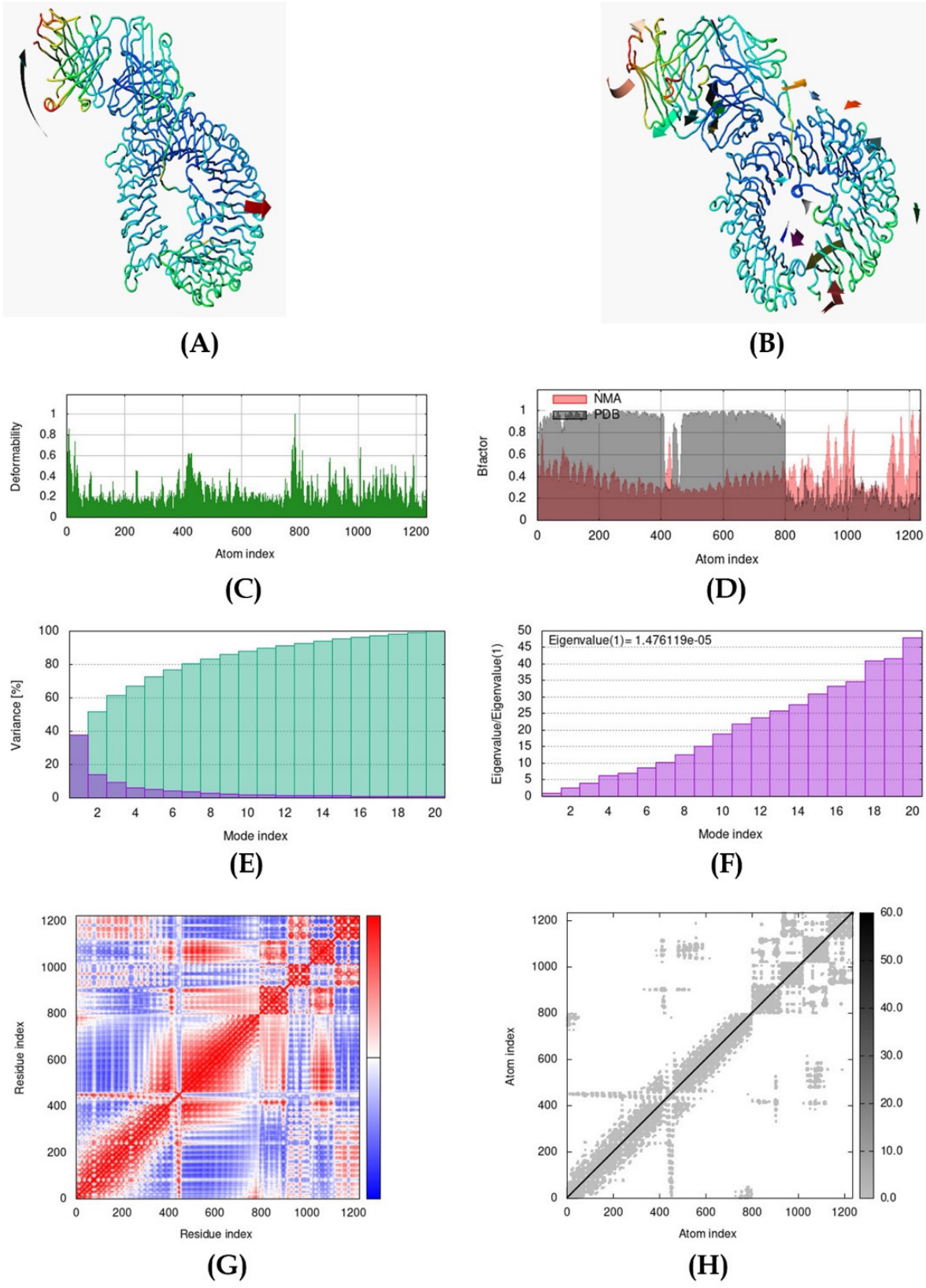

Figure 6. MD simulation output obtained from iMODS webserver of the docked complex.
MD: Molecular dynamics

Conclusion

Based on the findings of the present study, it can be concluded that Bevacizumab demonstrates significant promise as a mAb repurposing strategy for the treatment of SLE by acting as a potent TLR-7 antagonist. Furthermore, the exploitation of virtual repurposing of the available mAb as performed in this work could ease, fasten and, hence, enrich the discovery and approval of such specific biologics.

Ethics

Ethics Committee Approval: Not necessary.

Informed Consent: Not necessary.

Peer-review: Externally peer-reviewed.

Financial Disclosure: The author declare that he has no relevant financial.

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