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Chimeric Vaccine Design against Dengue Virus Using Immunoinformatics and Docking Approaches

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ABSTRACT

Background and Objective: Over the past five years, transmission of the dengue virus to humans by infected Aedes mosquitoes has increased significantly. Preventive methods such as developing an effective vaccine are the best option to combat dengue infection. The aim of this study is to develop chimeric vaccines against dengue viruses using immunoinformatics and molecular docking approaches.

Methods: In this in silico analysis**,** the genomic protein of dengue viruses was used to develop a recombinant multivalent epitope vaccine. 5 B cell lymphocyte (BCL) epitopes, 5 cytotoxic T lymphocyte (CTL) epitopes, and 5 helper T lymphocyte (HTL) epitopes, suitable adjuvant, and linkers were chosen in the structure of the final multi-epitope vaccine. The construct was analyzed computationally to predict antigenic, allergenic, and physiochemical properties as well as two- and three-dimensional structures. Finally, another analytical study was carried out by docking and in silico cloning.

Findings: Based on our findings, the designed vaccine with 320 residues has suitable antigenicity and physicochemical properties. Molecular docking simulations between the engineered vaccine construct and five Toll-like receptors (TLRs) revealed that the vaccine displays the strongest binding affinity and optimal docking conformation with TLR3 and TLR9. Furthermore, codon optimization analysis identified Escherichia coli strain K12 as a suitable host for improved linear DNA sequences.

Conclusion: Based on the results of this study, the final vaccine construct comprises 15 epitopes (5 B-cell epitopes, 5 CTL epitopes, and 5 HTL epitopes) along with an adjuvant. It is potentially antigenic and non-allergenic.

Keywords: *Vaccines, Dengue, Computer Simulation, Immunoinformatics, Fever, Docking*.

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Introduction

Dengue virus is a small, spherical, single-stranded RNA virus of approximately 11 kb in length, possessing an icosahedral envelope. It belongs to the family Flaviviridae (1, 2). Dengue virus comprises four antigenically distinct serotypes (DENV-1 through DENV-4), all of which are capable of causing human infection (3). This virus only replicates inside a host organism. Several processes are involved in the dengue virus life cycle such as attachment to the host cell surface, nucleocapsid release, virus replication, protein synthesis and processing, nucleocapsid formation, virus assembly, and the release of mature virus particles. A single polypeptide is created due to the translation of the viral RNA. 10 types of protein (3 structural proteins and 7 non-structural [NS] proteins) have critical roles in the structure and function of viruses. These key proteins are defined as follows: capsid protein (CP), envelope protein (EP), membrane protein (MP), NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. The structural proteins are primarily responsible for the assembly of viruses, while viral entry, replication, translation, regulation of vital processes, and pathogenesis of the virus depend on the function of non-structural proteins (1-4).

Dengue fever is among the most rapidly spreading arboviral diseases and is transmitted to humans through the bite of infected Aedes mosquitoes (primarily Aedes aegypti) (3). The rainy season is associated with a rise in dengue incidence, correlating with increased vector proliferation and dispersal. Several hundred million people are infected by this virus annually. Due to its geographical location and borders with dengue-endemic countries, Iran is considered a high-risk region for dengue virus introduction and transmission (5). Most of the infections caused by the dengue virus are asymptomatic and only 25% lead to obvious clinical symptoms (6, 7). Clinical manifestations vary depending on the serotype, host genetic factors, and viral virulence, and may include high fever, severe headache, intense myalgia, nausea, and vomiting (2, 8, 9). The increasing number of dengue virus infections represents a growing public health problem worldwide, driven by the virus's global distribution and the lethal consequences of severe disease (10, 11).

CYD-TDV was the first dengue vaccine to be licensed. Studies show that this vaccine may increase the risk of more severe disease in seronegative individuals (12). In the case of the TAK-003 vaccine, the effectiveness decreased over time (13). Additional concerns associated with dengue vaccines include mild rash as a side effect, reduced immunogenicity following low-dose immunization, and age-dependent variations in vaccine response (12, 13).

Currently, there is no effective antiviral drug against the dengue virus, and the medications prescribed are intended to relieve the symptoms of the disease (14). On the other hand, drug production has always been a very challenging, time-consuming, and expensive process (15). Therefore, the development of safe and effective vaccines against viral pathogens represents a fundamentally important strategy for preventing such infections (16). A well-established and rapid technique in this field involves constructing multi-epitope vaccines based on bioinformatics research and the vaccinomics approach. In this method, the main and key protein fragments of the virus are selected for filtering high-potential immunogenic, non-allergenic, and non-toxic epitopes. Integrated multi-epitope vaccines are constructed by adding adjuvants and linkers. Finally, the designed vaccine candidates require validation through in silico methods, which can predict their physicochemical properties and model their molecular interactions with key immunological receptors - thereby assessing their potential ability and effectiveness prior to laboratory testing (17, 18).

Given the importance of preventing viral infections, this study aimed to design a chimeric vaccine against dengue viruses using immunoinformatics and docking approaches.

Methods

This study was based on in silico analysis methods. The first step in the design of a multi-epitope vaccine is the selection of the target protein. To obtain the target protein's amino acid sequences in FASTA format, we used the UniProtKB database (https://www.uniprot.org/), a free resource for protein sequences. A crucial part of the antigen region that binds to an antibody or immunoglobulin is known as a B-cell epitope. Hence, in this study, suitable B-cell epitopes were selected with score > 0.90 using the server ABCpred. For prediction of CTL epitopes based on 11 supertypes (A1, A2, A3, A24, A26, B7, B8, B27, B29, B44, and B58), the binder sites were determined using the NetCTL server at http://www.cbs.dtu.dk/services/NetCTL/. Further analysis on CTL Epitopes was done to obtain IEDB alleles based on IC50 <500 nM using the Immune Epitope Database (IEDB). Finally, Helper T Lymphocyte (HTL) epitopes were predicted by IEDB. Filtering was done after selecting the full HLA reference set.

Epitopes with potential antigenic values are selected as suitable sequences for final vaccine design. On the other hand, epitopes should be non-allergic and non-toxic. For the study of antigenicity, toxicity, and allergenicity properties, we used the VaxiJen server (with a threshold of 0.4), the AllerTOP v.2.0 server (with 94% sensitivity), and the ToxinPred online server. Then, specific linkers were used to join the screened peptide sequences together to construct the vaccine sequence. The final multi-epitope vaccine construct was assembled by joining B-cell, CTL, and HTL epitopes using KK, AAY, and GPGPG linkers, respectively. To enhance immunogenicity, an adjuvant - the defensin-like protein (UniProt ID: P81534, 67 residues) - was fused to the N-terminus using a rigid EAAAK linker, which helps maintain functional domain separation.

Using a threshold value of 0.4, the VaxiJen v2.0 tool was employed to predict the antigenicity of the designed vaccine. The vaccine's allergenic potential was assessed using AllerTOP version 2.0. The ProtParam server was used to obtain the physicochemical properties of the construct, including molecular mass, number of amino acids, isoelectric point (pI), instability index, grand average of hydropathicity (GRAVY), and aliphatic index.

To obtain the distribution of alpha helices, 3_{10} helices, pi helices, beta bridges, extended strands, beta turns, random coils, and ambiguous states in the secondary structure, the self-optimized prediction method (SOPMA) was used. The I-TASSER web server was used to predict the three-dimensional structure of the designed vaccine. A Ramachandran plot was also generated using the Ram Plot Analysis server.

An in silico method to study the effectiveness of the developed vaccine in binding to Toll-like receptors (TLRs) is molecular docking simulations. The TLR3 (PDB ID:1ziw), TLR4 (PDB ID: 2z66), TLR7 (PDB code: 7CYN), TLR8 (PDB code: 3w3g), and TLR-9 (PDB ID: 3WPF) receptors were retrieved from the PDB site. The HDOCK server was used to study their interactions and docking scores. Water molecules and extra molecules were removed from receptors to facilitate the docking process. Following docking, the vaccine-receptor complexes were filtered to select the complex with the lowest binding energy. Discovery Studio 2024 Client was then used to visualize and analyze the interactions (e.g., hydrogen bonds, hydrophobic interactions) between the designed vaccine and the five receptors. Because codon optimization significantly influences protein expression, the BCCM/GeneCorner was used to construct the linear DNA sequences of the vaccine, and further optimization was carried out using the Java Codon Matching Tool (JCat).

Results

The amino acid sequence of the dengue virus polyprotein, with a length of 3391 residues and accession number Q9WDA6, was downloaded in FASTA format. This polyprotein contains both structural and non-structural proteins.

After using the ABCpred, NetCTL, and IEDB servers, three types of epitopes (B-cell, CTL, and HTL) were selected. From these, non-allergenic and non-toxic sequences with suitable antigenicity levels were filtered for the construction of a multi-epitope subunit vaccine. The final selected epitopes of each type are listed in Table 1.

Table 1. List of final peptide sequences from three types of epitopes

B-cell epitopes					
Peptide Sequence	**Start position**	**Score**	**Antigenicity**	**ALLergenicity**	**Toxicity**
MVMVGATMTDDIGMGV	1184	0.96	1.0789	NA	NT
IGVIITWIGMNSRSTS	739	0.94	1.3065	NA	NT
YGTVTMECSPRTGLDF	458	0.94	1.0978	NA	NT
KGKRIEPSWADVKKDL	36	0.95	1.2132	NA	NT
RRLTIMDLHPGAGKTK	161	0.94	1.5056	NA	NT

CTL epitopes					
Peptide Sequence	**Start position**	**NetCTL allels**	**IEDB allels (IC50<500 nM)**	**Antigenicity**	**ALLergenicity and Toxicity**
LMMRTTWAL	2425	A2,A24,B8,B39,B58,B62	HLA-A*02:01 HLA-A*02:06 HLA-B*08:01 HLA-A*02:03 HLA-A*32:01 HLA-B*15:01 HLA-B*35:01	1.1235	NA/NT
FRKRRLTIM	1658	B8,B27	HLA-B*08:01	1.1135	NA/NT
ETACLGKSY	3241	A1, B26,B62	HLA-A*26:01	0.8757	NA/NT
GSAKLRWFV	2549	A1	HLA-A*68:02 HLA-A*02:06 HLA-A*30:01	0.6448	NA/NT
QEHETSWHY	2777	A1,B44,B62	HLA-B*44:03 HLA-B*44:02	0.9286	NA/NT

HTL epitopes					
Peptide Sequence	**Start position**	**IEDB ALLELE**	**Antigenicity**	**ALLergenicity**	**Toxicity**
GMGVTYLALLAAFK	1195	HLA-DRB1*01:01 HLA-DRB5*01:01 HLA-DRB1*04:05 HLA-DRB1*15:01 HLA-DRB1*11:01 HLA-DPA1*03:01/DPB1*04:02	1.1007	NA	NT

		HLA-DQA1*05:01/DQB1*03:01 HLA-DRB1*09:01 HLA-DRB1*04:01 HLA-DRB1*07:01 HLA-DPA1*01:03/DPB1*02:01 HLA-DRB4*01:01 HLA-DPA1*02:01/DPB1*01:01 HLA-DPA1*01:03/DPB1*04:01 HLA-DRB1*08:02			
LALKEFKEFAAGRKS	2080	HLA-DRB5*01:01 HLA-DRB1*15:01 HLA-DRB1*01:01 HLA-DQA1*04:01/DQB1*04:02 HLA-DRB1*11:01 HLA-DRB1*09:01	0.8187	NA	NT
GAKRMAILGDTAWDF	688	HLA-DRB3*01:01 HLA-DRB1*03:01 HLA-DQA1*05:01/DQB1*02:01 HLA-DRB1*01:01	1.1193	NA	NT
GKIVQPENLEYTVVI	407	HLA-DPA1*03:01/DPB1*04:02	0.8959	NA	NT
TGNMSFRDLGRVMVM	1172	HLA-DRB1*11:01 HLA-DRB1*01:01 HLA-DRB5*01:01 HLA-DQA1*04:01/DQB1*04:02 HLA-DRB1*08:02 HLA-DRB1*07:01 HLA-DRB4*01:01 HLA-DRB1*13:02 HLA-DRB1*15:01	1.1141	NA	NT

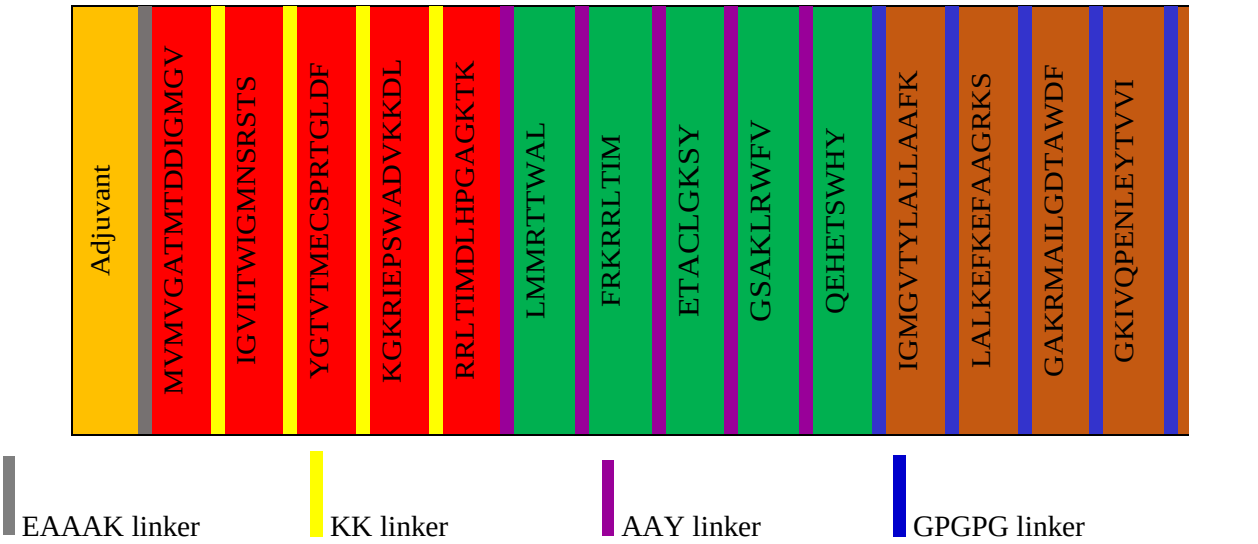
*NA: Non-Allergic; NT: Non-Toxic

The final multi-epitope subunit vaccine was constructed using a defensin-like protein as an adjuvant, along with a total of five B-cell epitopes, five CTL epitopes, and five HTL epitopes. The epitopes were linked using EAAAK, KK, AAY, and GPGPG linkers. The complete construction of the final vaccine construct is illustrated in Figure 1.

Analysis using the Vaxijen V2.0 and AllerTOP V2.0 servers revealed that the designed vaccine is non-allergenic, with an antigenicity score of 0.7859. Further characterization via the ProtParam server yielded the following parameters: molecular mass, 35.005 kDa; total number of amino acids, 320; isoelectric point (pI), 10.04; instability index, 34.60; grand average of hydropathicity (GRAVY), -0.144; and aliphatic index, 75.97.

Secondary structure analysis using the SOPMA server revealed that the designed vaccine, comprising 320 amino acids, contains 109 residues (34.06%) participating in alpha helix formation, 68 residues (21.25%) in extended strands, and 143 residues (44.69%) in random coil structures. For three-dimensional structure prediction, the I-TASSER server generated five final models. Among these, the model with a C-score of -4.74, an estimated TM-score of 0.23±0.06, and an estimated RMSD of 18.5±2 was selected.

The predicted secondary structure, three-dimensional structure, and Ramachandran plot of the designed vaccine are presented in Figure 2, Figure 3, and Figure 4, respectively.



MRIHYLLFALLFLFLVPVPGHGGIINTLQKYYCRVRGGRCAVLSCLPKEEQIGKCSTRGRKCCRRK
KEAAAK
MVMVGATMTDDIGMGVkkIGVIITWIGMNSRSTSkkYGTVTMECSPRTGLDFkkKGKRIEPSWAD
VKKDLkk
RRLTIMDLHPGAGKTKAAYLMMRTTWALAAYFRKRRLTIMAAYETACLGKSYAAYGSAKLRW
FVAAY
QEHETSWHYGPGPGIGMGVTYLALLAAFKGPGPGLALKEFKEFAAGRKSGPGPGGAKRMAILGD
TAWDFGPGPG GKIVQPENLEYTVVIGPGPGTGNMSFRDLGRVMVM

Figure 1. The construction of a final multi-epitope subunit vaccine

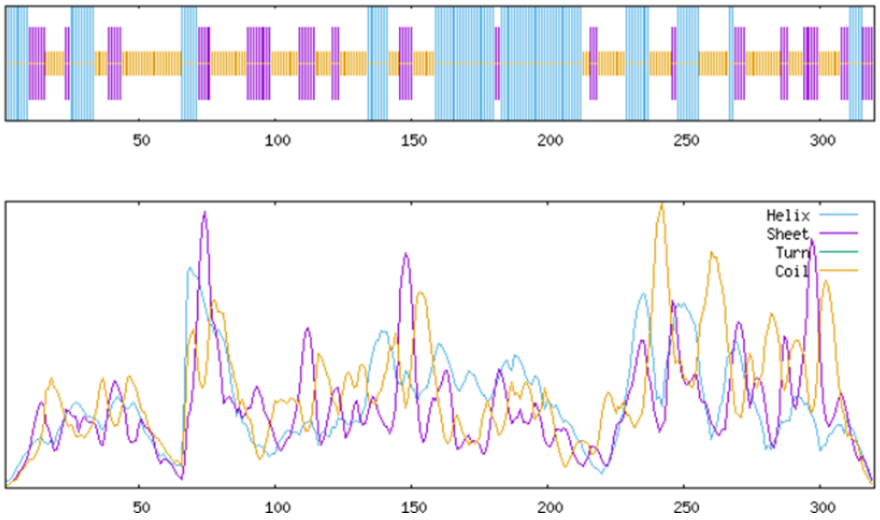


Figure 2. The predicted two-dimensional structure of the designed vaccine

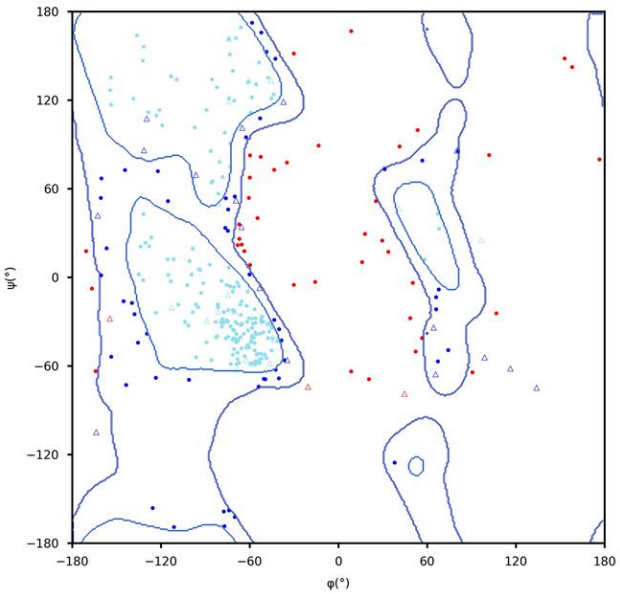


Figure 3. Standard 2D Ramachandran Plot. Cyan, blue, and red (dots/triangles) represent torsion angles of favored, allowed, and disallowed regions respectively; dots represent residues other than glycine, and triangles represent glycine.

Molecular docking between the designed vaccine and Toll-like receptors (TLRs) was performed using the HDOCK server. For each receptor, the lowest energy value among the ten best conformations was selected. The minimum energy values for the complexes were as follows: 1ziw-vaccine, -374.58; 2z66-vaccine, -342.73; 7CYN-vaccine, -324.85; 3w3g-vaccine, -305.60; and 3WPF-vaccine, -353.43. The docking results were visualized and analyzed using Discovery Studio 2024 Client. The optimal conformation of the complex comprising the vaccine and the five receptor types is illustrated in Figure 4.

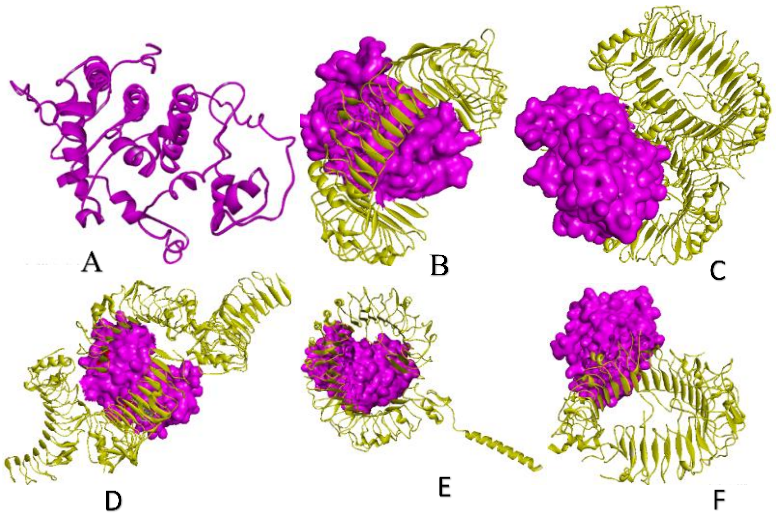


Figure 4. (A) Three-dimensional structures of designed vaccine, (B) optimal conformation of 1ziw-vaccine complex, (C) optimal conformation of 3w3g-vaccine complex, (D) optimal conformation of 2z66-vaccine complex (E) optimal conformation of 7CYN-vaccine complex , (F) optimal conformation of 3WPF-vaccine complex

Finally, the 320-amino-acid sequence was reverse-translated into a 960-base nucleotide sequence using the most likely codons. According to the JCAT online server, Escherichia coli strain K12 (E. coli str. K12) was identified as a suitable host for the optimized linear DNA sequence, which exhibited a GC content of 56.67% and a Codon Adaptation Index (CAI) of 0.94.

Discussion

The final vaccine, which was based on 15 epitopes (5 B-cell epitopes, 5 CTL epitopes, and 5 HTL epitopes) and adjuvants, was potentially antigenic and non-allergenic. The dominant secondary structure of the designed vaccine was made up of alpha helix and random coils. "Structural antigens" include naturally unfolded protein regions and convoluted helical motifs. An increase in these two structures may enhance the detectability of antibodies produced following infection (19). Research by Cespedes et al. demonstrates that α-helical coiled-coil structures in pathogens stimulate the production of specific antibodies (20).

The isoelectric point and instability index of the final structure indicate the basic nature and stability of the vaccine. The computed grand average of hydropathicity (GRAVY) value shows that the designed vaccine is hydrophilic, which may enhance protein-protein interactions and water solubility. Consistent with these findings, Tahir ul Qamar et al., who worked on epitope-based peptide vaccine design, reported that the hydrophilic regions of proteins are generally exposed on the surface and play a significant role in eliciting immune responses (21). Furthermore, effective cellular and humoral immune responses against the target pathogen require the binding of vaccine structural molecules to host immune receptors.

Docking studies between the developed vaccine and TLRs demonstrated that the vaccine interacts well with all five types of receptors. The order of binding affinity was as follows: TLR3 (PDB ID: 1ziw)> TLR-9 (PDB ID: 3WPF) >TLR4 (PDB ID: 2z66)>TLR7 (PDB code: 7CYN)> TLR8 (PDB code: 3w3g). The best binding affinity and conformational stability were observed for the TLR3-vaccine and TLR9-vaccine complexes. An important part of pathogen recognition and activation of innate immunity is performed by TLR3 (22). Most viral infections produce double-stranded RNA (dsRNA), for which TLR3 is a good receptor (22-26). Upon detection of dsRNA oligonucleotides, TLR3 activates IRF3, leading to increased production of type-I interferons (IFNs), which in turn exert effects on T cells (22, 27).

All of these pathways eventually lead to enhanced antiviral activity in the defense system. 13 residues of TLR3 are implicated in the formation of hydrogen bonds with our vaccine candidate, including ASP280, ASN229, ARG331, LYS335, ASP364, TYR307, SER206, GLU639, HIS39, HIS156, LYS330, GLU203, and PHE84.

TLR9 is found in endosomes, lysosomes, and the endoplasmic reticulum (28). Due to its characteristics, this receptor only interacts with foreign DNA. Bacterial and viral DNA frequently contains unmethylated CpG motifs, which can be recognized by TLR9 (29, 30). 6 amino acids of TLR9 are implicated in the formation of hydrogen bonds in the vaccine-TLR9 interaction, including ASP650, ASN599, PHE569, HIS574, GLY627, and TYR537. Codon optimization was performed to ensure expression of the developed vaccine in a specific expression system. Based on the results, E. coli str. K12 was determined to be a suitable host for the optimized linear DNA sequences.

In this study, multiple in silico and immunoinformatics techniques were successfully used to develop a chimeric vaccine targeting the dengue virus and verify its properties. Nonetheless, future studies should include in vitro and in vivo experiments to evaluate the safety and efficacy of this vaccine construct.

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