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In Silico Analysis of Bioactive Compounds From Moringa Oleifera Leaves For Inhibiting The Latent Membrane Protein-1 (LMP-1) of The Epstein-Barr Virus Which Causes Nasopharyngeal Cancer

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ABSTRACT

Background: Nasopharyngeal carcinoma (NPC), closely linked to Epstein-Barr virus (EBV) infection, is prevalent in Southeast Asia, with EBV's Latent Membrane Protein-1 (LMP1) playing a crucial role in cancer progression. The current treatment options for NPC are limited, and the need for novel therapeutic strategies targeting LMP1 is urgent. **Aim:** This study employed in silico approaches to identify potential LMP1 inhibitors from Moringa oleifera bioactive compounds. **Methods :** Protein structure prediction was performed using AlphaFold, followed by binding site identification using PrankWeb.cz. Molecular docking analysis was carried out using PLANTS software to assess the binding affinity of selected compounds. QSAR analysis was used to correlate molecular descriptors with biological activity. **Results:** The study found that compounds such as Thiamine and Indole-3-Acetonitrile exhibited strong binding affinities with LMP1, demonstrated by low docking scores (e.g., Thiamine: -57.951). The QSAR analysis further revealed favorable properties for these compounds, suggesting good bioavailability and potential for LMP1 inhibition. **Conclusion:** This study successfully identified promising Moringa oleifera compounds as potential inhibitors of LMP1 in EBV-associated NPC using computational tools. These findings provide a foundation for future experimental validation and the development of natural product-based therapies for EBV-related cancers.

Keywords: *Bioactive compounds, Epstein-Barr virus, in silico screening, Latent Membrane Protein-1 (LMP1), Moringa oleifera, Nasopharyngeal carcinoma.*

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is one of the most common head and neck cancers in Southeast Asia, including Indonesia, with the latest statistics reporting that it has a high incidence, reaching 6.2 per 100,000 population, and approximately 13,000 new cases each year [1]. In Indonesia, NPC ranks fifth among cancer-related deaths, as most cases are diagnosed at an advanced stage due to nonspecific early symptoms, leading to a low survival rate [2]. NPC has several identified risk factors. However, the Epstein–Barr virus (EBV) plays a central role as the primary risk factor, particularly in non-keratinizing differentiated types (WHO types II and III), with nearly 100% of cases being EBV-positive in endemic regions [3].

The Epstein–Barr virus (EBV) Latent Membrane Protein-1 (LMP-1) is a primary oncoprotein of EBV, capable of mimicking the CD40 receptor and involved in activating the NF-κB, JAK/STAT, PI3K/AKT, and MAPK pathways, thereby inducing cell proliferation, apoptosis inhibition, invasion, and metastasis in NPC carcinogenesis. LMP-1 is expressed latently in EBV-infected nasopharyngeal epithelial cells, promoting cancer cell progression, contributing to radiation resistance during treatment, and leading to poor prognosis, as it can interact with cancer related proteins such as tumor necrosis factor receptor-associated factors (TRAFs) and interferon regulatory factor 7 (IRF7) [4,5]. A strong association has been reported between LMP-1 expression and poor prognosis in advanced NPC, with 82.5% of advanced-stage cases exhibiting positive LMP-1 expression showing reduced survival [6].

The consumption of salted fish and fermented foods increases the risk of latent EBV progressing to malignancy, as reported in a study from Indonesia, where the prevalence of NPC showed a male-to-female ratio of 2.4:1 and a peak incidence at 40–60 years of age [7]. The standard therapy for NPC remains radiotherapy combined with chemotherapy, such as cisplatin. However, LMP-1's resistance to apoptosis reduces treatment effectiveness, highlighting the need for novel molecular targets [8]. One promising targeted therapy involves inhibiting LMP-1, particularly through peptide inhibitors directed at its C-terminal activating regions (CTAR) domain, which have the potential to disrupt oncogenic signaling and restore immune surveillance [9].

Moringa oleifera is a tropical plant rich in phytochemicals, offering broad anticancer potential due to various compounds, including quercetin, kaempferol, isothiocyanates, glucosinolates, and niazimicin, which have been reported to inhibit cell proliferation in various cancers, including breast, colorectal, liver, lung, prostate, and oral cancers, by inducing apoptosis through Bcl-2/Bax, caspases, and reactive oxygen species (ROS) mechanisms [10]. M. oleifera leaf extract has also been reported to slow tumor progression through anti-inflammatory and anti-metastatic effects by downregulating the expression of inflammatory mediators, including tumor necrosis factor (TNF-α), heat shock protein-27 (HSP27), and interleukin-10 (IL-10) [11]. In vitro and in vivo studies have shown that Moringa leaf nanoparticles inhibit lipase, DPP4, and α-glucosidase, further demonstrating broad-spectrum anticancer potential [12]. Hence, targeting LMP-1 using natural products, such as those found in Moringa oleifera extracts, could potentially be developed as anticancer agents or as supportive therapies in NPC treatment.

Previously, in silico approaches have successfully investigated the potential of M. oleifera compounds as antiviral inhibitors against SARS-CoV-2 Mpro and NDV, as well as anticancer agents targeting HIF-1α, VEGF, and GLUT-1 in breast cancer, and KRAS G12C in colorectal cancer. The results showed strong binding affinities, such as quercetin (-9.37 kcal/mol) [13,14]. Although no direct studies have been conducted on LMP-1, other M. oleifera phenolic compounds, such as β-sitosterol and catechin, exhibit high affinity for viral targets and oncoproteins, supporting the potential of these compounds against LMP-1 and highlighting the need for molecular docking screening [15].

In silico studies enable prediction of interactions between M. oleifera bioactive compounds and the functional domains of LMP-1 (CTAR1/2/3), including docking analysis, molecular dynamics, ADMET, and pharmacophore modeling for the identification of potential lead compounds [9]. This approach is crucial prior to subsequent in vitro testing, as it helps save time and cost while predicting toxicity and bioavailability. In Indonesia, integrating herbal medicines such as Moringa with conventional therapies aligns with national health priorities for treating endemic cancers 1.

This study aims to screen the bioactive compounds of M. oleifera against the LMP-1 structure using Alphafold.com, followed by Protein validation, Redocking via YASARA and PLANTS Software, Visualisation with Discovery Studio 2025 and pharmacopore identification using pharmitt.csb to explore their anticancer properties against NPC. Selected active compound profed by high docking score continued with QSAR determination using BuildQSAR and HyperChem to establish the relationship

between descriptor parameters (molecular orbitals) and biological activity, represented by docking scores. The hypothesis is to exploring and modelling the *moringa oliefera* chemical compound as a potent inhibitor agent to LMP-1 of the EBR Virus, with stable RMSD <2 Å and binding energy < -7 kcal/mol. These findings could contribute to the development of natural product-based drugs for treating EBV-positive NPC, supporting the advancement of anticancer therapeutics derived from tropical plants.

MATERIALS AND METHODS

Protein Structure Validation

This study began with the utilization of Alphalold.com , a bioinformatics tool for predicting the three-dimensional structure of the LMP1 protein. Two UniProt codes were initially considered: R5D174 and D8DV78. To improve docking accuracy, the study focused solely on the R5D174 protein structure, which had a confidence level of 95.772%, ensuring that the predicted structure is both accurate and biologically relevant. Once the protein structure was predicted, potential binding sites were identified. Since LMP1 lacks a native ligand, the binding site was predicted using PrankWeb.cz, which generated grid box coordinates approximately at (-17.1114, -11.0999, 29.8953) with dimensions of 40 × 40 × 40. Based on the predicted LMP1 structure, the study proceeded with further computational analyses. After determining the binding site, RMSD (Root Mean Square Deviation) calculations are used using PLANTS software for docking purposes and YASARA software to produced an RMSD value of 1.28 Å, indicating that the docking protocol is reliable for predicting stable ligand–protein interactions.

Pharmacophore Modeling

Following the re-docking and validation of the binding site, pharmacophore modeling was employed to identify bioactive compounds from M. oleifera capable of interacting with LMP1. Based on previous findings by Susantiningsih et al. (2025), eight compounds derived from Moringa leaves were selected and optimized as potential LMP1 inhibitors. Pharmacophore modeling predicted the active sites of each ligand based on chemical properties, including hydrophobicity, hydrogen-bonding potential, and electrostatic interactions. Selected compounds included ascorbic acid, niacin, and thiamine, which were analyzed for their interactions with LMP1. The results revealed that these compounds have potential to inhibit LMP1 activity and were thus prioritized for further molecular docking analysis.

Molecular Docking

Molecular docking was performed using PLANTS (phyton programming language version 1.1) to evaluate the binding affinity of selected ligands toward LMP1. Ligand and protein preparation was assisted by YASARA version 19.7.20 and MarvinSketch software version 14.11.3.0 to ligand preparation, allowing accurate representation of ligand–receptor interactions. Each compound was tested with ten conformers, and the minimum energy was calculated to identify the lowest-energy conformation. Docking results showed that some compounds, such as thiamine, exhibited very low docking scores (e.g., -57.951), indicating strong interactions between the ligand and protein and suggesting thiamine as a potential candidate for LMP1 inhibition.

Docking Visualization

Docking results were visualized using Discovery Studio Visualizer version 25.1.0.24284 to provide graphical representations of ligand–LMP1 interactions. Visualization revealed how ligands bind to the protein's binding site, Hydrogen bond surface mapping and highlighting key residues involved in the 2D and 3D interaction. For example, thiamine formed hydrogen bonds with residues such as asparagine, phenylalanine, and leucine, further supporting the docking results and demonstrating the ligand's potential as an LMP1 inhibitor.

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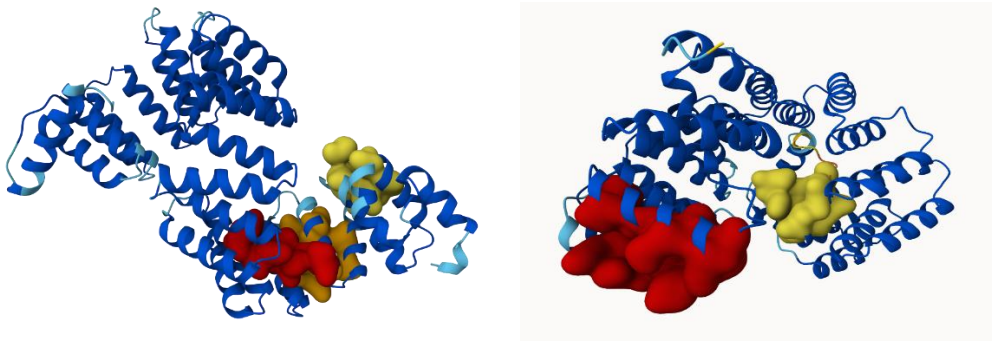
QSAR (Quantitative Structure–Activity Relationship) Analysis

QSAR analysis was conducted to further elucidate the relationship between the chemical structure of bioactive compounds and their biological activity. Molecular descriptors, including HOMO, LUMO, LogP, and total energy, were calculated to predict bioactivity and pharmacokinetic properties. The analysis showed that compounds such as indole-3-acetonitrile and thiamine possess favorable QSAR properties, indicating good bioavailability, which may lead to increased effectiveness as LMP1 inhibitors. QSAR analysis using HyperChem for Windows Molecular Modelling System version 8.0.10 and BuildQSAR version 2.1.0.0.

RESULTS

Protein Validation

The Latent Membrane Protein-1 (LMP1) for the Epstein-Barr virus is still rarely studied, as evidenced by the limited empirical evidence that could serve as an LMP1 inhibitor mechanism. The discovery of drugs based on the macromolecular structure of LMP1 is called SBDD, which has a high-accuracy exploration function. The first step is the virtual screening process of the protein structure using Alpha Fold with uniprot codes R5D174 & D8DV78, but this study will only use one protein structure code to improve the accuracy of the docking process based on a high confidence value (95.772). The protein does not have an active native ligand, so the binding site must be predicted using PrankWeb.cz, resulting in a grid box of approximately (-17.1114, -11.0999, 29.8953) and dimensions (40;40;40) for a total of 13 amino acid residues (chain A). After determining the binding site, the RMSD calculation was performed using the PLANTS software thru the Re-Docking process, yielding a value of 1.28 Å.



(a) (b)

Figure 1. Predictive pocket site in LMP1-EBV (a) Uniprot: D8DV78; (b) Uniprot: R5D174

Using AlphaFold and PrankWeb.cz, two bioinformatics tools, the authors identified several predictive pocket sites on the LMP1 protein (Figure 1 and Table 1). These sites represent regions where small molecules (ligands) are expected to interact with the protein. The results show that the AlphaFold confidence score for these binding sites is high, with a value of 95.7% for the LMP1-B protein (UniProt: R5D174). This high confidence indicates that these sites are likely biologically relevant and suitable for drug binding.

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Table 1. Detailed information about LMP1-EBV in Alpha Fold and PrankWeb.cz

Uniprot : D8DV78 (LMP1-A)						
Rank	**Score**	**Probabilty**	**Pocket center**	**Armstrong**	**#Residues (amino acid)**	**AlphaFold Confidence**
1	3.26	0.098	(-15.6041, 1.0258, 12.1491)	347.4	8	95.469
2	2.40	0.052	(-1.3208, 8.6191, 29.6285)	275.3	8	78.326
3	1.83	0.030	(-18.6940, 12.0193, 21.0574)	273.3	9	94.089
Uniprot : R5D174 (LMP1-B)						
Rank	**Score**	**Probabilty**	**Pocket center**	**Armstrong**	**#Residues (amino acid)**	**AlphaFold Confidence**
1	3.32	0.102	(-17.1114, 11.0999, 29.8953)	878.8	13	95.722
2	2.40	0.047	(7.3423, 6.7699, 17.8058)	346.3	9	78.261

Pharmacopore Model

Based on the previous screening and optimization of ligands from moringa leaves by 16, 8 compounds with a toxicity level of class 6 (relatively non-toxic) were identified. Modeling using pharmacophore also supports the compound filtration process for use with characteristics other than its pharmacodynamics, namely in terms of the active site of the compound. The pharmacophore model is closely related to the results of 2D docking visualization because it will interpret the number of amino acids binding to the ligand's active site.

This study selects eight compounds, including Ascorbic Acid, Niacin, and Thiamin, for their potential as LMP1 inhibitors. Pharmacophore modeling was used to predict the active site of each ligand based on its chemical characteristics such as hydrophobicity, hydrogen bonding, and electrostatic interactions (Figure 2). The ligands were analyzed for their interactions with the LMP1 protein based on these descriptors, and compounds that showed favorable interactions were prioritized for further docking studies.

Molecular Docking

Docking uses the PLANTS (Protein Ligand ANT Systems) program based on the docking score value, which describes hydrophobic interactions, hydrogen bonds, steric interactions, and the geometric contribution of the ligand according to the ChemPLP (Chemical Piecewise Linear Potential) function. Therefore, the preparation of ligands and proteins uses the YASARA and Marvin Sketch software because they can chemically depict the interaction between the ligand and the receptor, do not

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account for solvent contribution (no water), and are not based on the magnitude of activation energy. Each single compound is formed into 10 conformers with the lowest energy minimization using Avogadro and Marvin Sketch. The highest docking score relatively describes the ranking of the best ligand pose in each conformer.

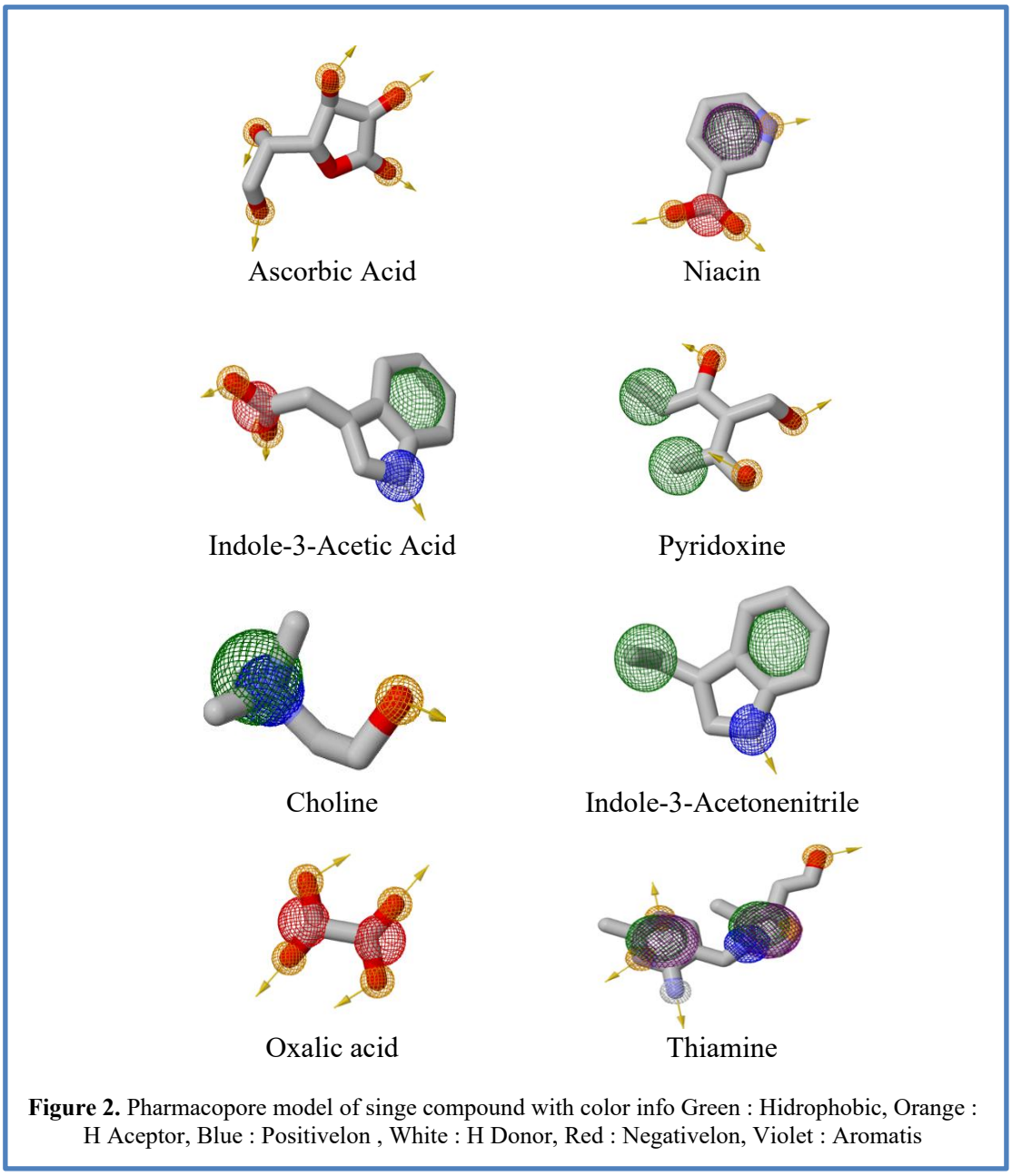


Figure 2. Pharmacopore model of singe compound with color info Green : Hidrophobic, Orange : H Aceptor, Blue : Positivelon , White : H Donor, Red : Negativelon, Violet : Aromatis

The focus of this study is on molecular docking, which was performed using the PLANTS software. Docking is a computational technique used to predict the preferred orientation of a ligand when binding to a receptor, in this case, the LMP1 protein. The docking score (Table 2) represents the binding affinity of the ligand, with more negative values indicating stronger binding. For example, thiamine shows the best docking score of -57.951, followed by Indole-3Acetonenitrile with a score of -50.993, indicating that these compounds are the most promising candidates for inhibiting LMP1.

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Table 2. The docking score for each active compound against the LMP1 protein.

Compounds	The Best Conformer	Docking Score	RMSD (Å)
Ascorbic Acid	3	-42.434	0.695
Choline	2	-34.159	0.631
Indole-3-Acetic Acid	10	-49.669	0.733
Indole-3Acetonenitrile	8	-50.993	0.425
Niacine	1	-37.977	0.614
Pyridoxine	5	-44.554	0.000
Thiamine	10	-57.951	0.000
Oxalic acid	5	-36.209	0.596

The molecular docking visualization (Figure 3) provides a graphical representation of the interactions between the ligand and the LMP1 protein. These images help illustrate how the ligand fits into the protein's binding pocket, highlighting key residues involved in the interaction. For example, thiamine shows a favorable ligand pose by forming hydrogen bonds with critical amino acids at the binding site (Asparagine, Phenylalanine, and Leucine). Visual confirmation of this docking position reinforces the interpretation of the docking results, indicating that the ligand binds in a manner that is likely to inhibit the function of the LMP1 protein.

Table 3. QSAR analysis of predicting compound (moleuclar orbital)

Compounds	Docking score	Molecular Description			
		HOMO	LUMO	Log P	Total E. (Kcal/mol)
Ascorbic Acid	-42.434	-10,323	-0,581	12,570	-106239,210
Choline	-34.159	-10,402	-0,666	11,450	-113010,130
Indole-3-Acetic Acid	-49.669	-10,291	-0,509	11,580	-113009,680
Indole-3Acetonenitrile	-50.993	-9,524	-0,653	11,110	-110334,070
Niacine	-37.977	-9,464	-0,557	11,230	-110333,610
Pyridoxine	-44.554	-10,384	-0,652	10,470	-119781,30
Thiamine	-57.951	-9,477	-0,628	9,770	-114428,570
Oxalic acid	-36.209	-9,500	-0,643	10,120	-117104,550

QSAR Properties

The molecular docking results for compounds as LMP1 inhibitors in Epstein-Barr Virus show variations in docking scores and differences in the interaction patterns of LMP1 amino acid residues. These variations suggest that the chemical structure characteristics of each compound play a role in determining the strength and stability of the ligand-protein interaction, based on the principles of Structure-Based Drug Design (SBDD). While molecular docking can provide an initial screening

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regarding the potential binding affinity (docking score) and ligand orientation to the receptor, further analysis is still required to identify structural parameters that significantly contribute to inhibition activity. QSAR analysis includes several molecular descriptors, such as HOMO (Highest Occupied Molecular Orbital), LUMO (Lowest Unoccupied Molecular Orbital), LogP (Partition Coefficient), and Total Energy. These descriptors are important for understanding the electronic properties and solubility of compounds, which influence their bioactivity.

QSAR analysis is used to establish the relationship between descriptor parameters (molecular orbitals) and biological activity, represented by docking scores. This approach is employed to develop a more accurate predictive model for the development of lead compounds in a more comprehensive manner.

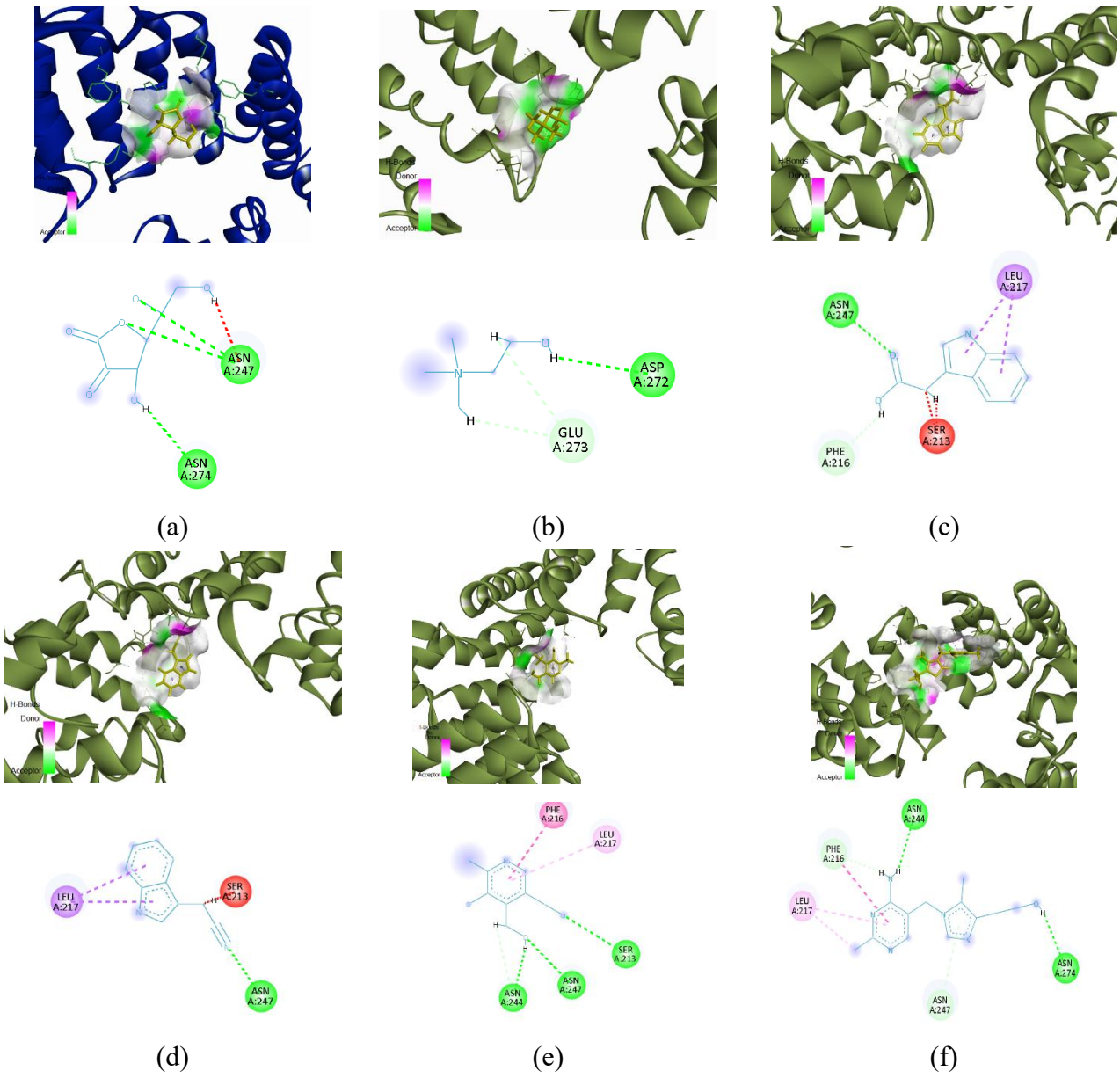


Figure 3. Molecular Docking visualization using Discovery Studio (a) Ascorbic acid; (b) Choline; (c) Indole-3Acetic Acid; (d) Indole-3-Acetonenitrile; (e) Pyridocxine; (f) Thiamine

This study found that compounds with more negative docking scores (table 3), such as Indole-3-Acetonitrile and Thiamine, also exhibit favorable QSAR properties. For example, Indole-3-Acetonitrile

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has a LogP value of 11.11, indicating that it is sufficiently lipophilic to cross cell membranes and reach its target, while Thiamine has a relatively lowest LogP value of 9,70, suggesting a slightly less favorable pharmacokinetic profile. The correlation between docking scores and QSAR properties indicates that these compounds likely have good bioavailability and are suitable for further development as potential LMP1 inhibitors.

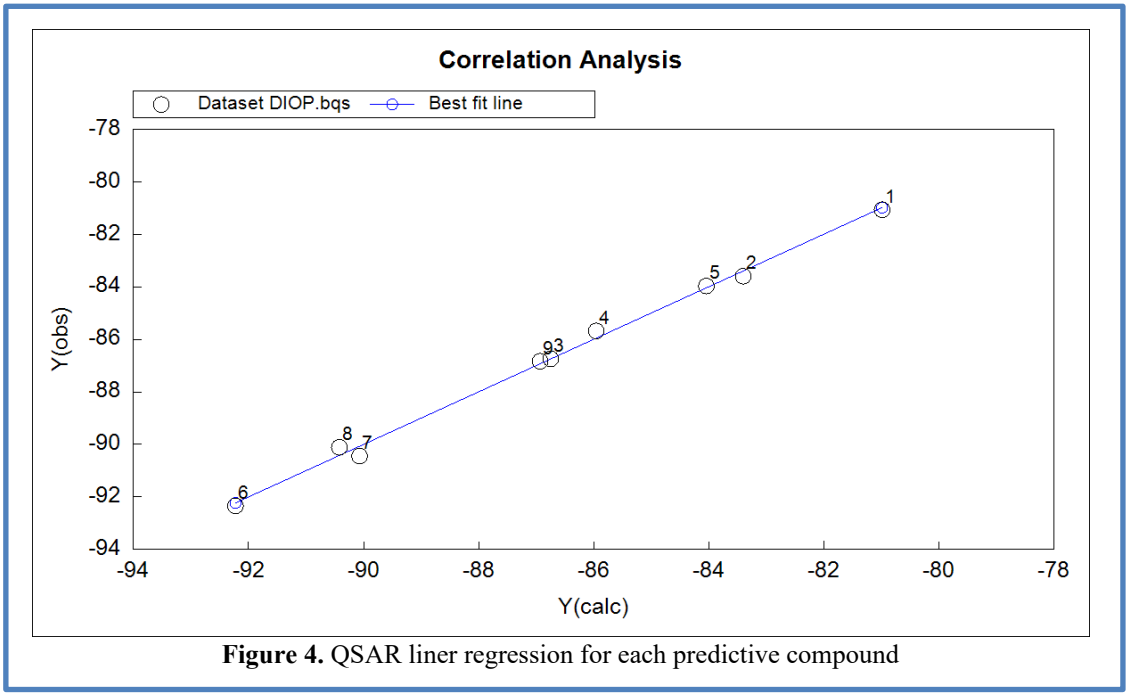


Figure 4. QSAR liner regression for each predictive compound

The graph of the line equation (Fig.4) shows a good correlation and linearity across the 9 data points represented by the modified compounds. The equation aims to determine the correlation between the observed docking score (obs) and the QSAR-calculated docking score (calc). The QSAR line equation is useful for predicting which atomic positions are more stable for attaching functional groups to the Epstein-Barr Virus receptor through the inhibition process (LMP1).

DISCUSSION

This study focuses on validating the computational approach used to identify potential binding sites and inhibitor compounds for the Latent Membrane Protein-1 (LMP1) of the Epstein-Barr Virus (EBV). The results of the study show that bioinformatics tools such as AlphaFold and PrankWeb.cz can accurately predict the binding sites on LMP1 with a high confidence level (95.7%), demonstrating its potential biological relevance in drug development. This is consistent with previous studies that have used computational predictions to identify binding sites on proteins of other viruses, such as HIV and influenza (Soltani et al., 2021). Similarly, in the context of EBV, the use of this pharmacophore model provides a rational basis for compound selection based on molecular properties and chemical interactions, serving as an initial step toward experimental validation.

The application of the pharmacophore model in this study also aligns with previous research that has used a similar approach to design virus protein inhibitors. For example, Kumar et al. (2022) used a pharmacophore model to identify inhibitor compounds for the SARS-CoV-2 protease, demonstrating the effectiveness of this model in the context of other virus targets 17. Similarly, in the context of EBV, the pharmacophore model provides a rational basis for selecting key compounds based on their molecular properties, which can help guide experimental validation and optimization.

The docking scores obtained in this study also reflect similar results to previous studies that have used molecular docking techniques to predict ligand binding affinity to target proteins. Research by

Xiong et al. (2022), which identified inhibitors for the NS2B-NS3 protease in the Zika virus, also showed that compounds with lower docking scores have higher binding affinity, similar to the findings in this study 18. The docking results for compounds such as Ascorbic Acid, which showed a score of -42.434 with an RMSD of 0.695 Å, indicate stability and reliability in predicting ligand binding positions. The low RMSD value reflects the consistency and reproducibility of ligand positioning, reinforcing the reliability of the docking protocol used in this study.

The docking visualization performed using Discovery Studio software aligns with previous studies that have used visualization to reinforce computational results. For instance, Zhang et al. (2022) used docking visualization to confirm the binding of small molecules to the SARS-CoV-2 spike protein, validating their computational results 19. In this study, docking visualization provides a clear view of how the ligand interacts with the LMP1 protein, clarifying the potential of the compounds as inhibitors and offering deeper insights into the binding mechanism that can aid in further drug design.

Furthermore, the QSAR analysis conducted in this study demonstrates the correlation between molecular descriptors, such as HOMO, LUMO, LogP, and Total Energy, and the biological activity of the compounds. These findings are consistent with previous studies that have integrated QSAR analysis to predict the antiviral activity of compounds against other virus targets, such as the research by Song et al. (2023) on SARS-CoV-2 protease inhibitors 20. The integration of molecular docking and QSAR analysis in this study enhances the selection of antiviral compounds by predicting the bioactivity and stability of the compounds, providing additional insights into the chemical and pharmacokinetic properties of the compounds with the greatest potential to inhibit LMP1.

CONCLUSION

The results of this study confirm that the applied computational approach, including the use of AlphaFold, PrankWeb.cz, pharmacophore modeling (pharmitt.csb), molecular docking, and QSAR analysis, provides a powerful tool for investigating bioactive compounds from *M. oleifera* as potential inhibitor agent of LMP1 in the EBV virus. Based on compound prediction and QSAR analysis prove that thiamine are predicted and favorable used for active pharmaceutical compound as potential inhibitors of LMP1 in the EBV virus. It have the highest docking score (-57.951), good hydrogen bond surface with amino acid and lowest Total energy (-119781,30 kcal/mol). These findings hold significant potential for the development of more effective therapies for diseases associated with EBV and make an important contribution to the field of structure-based herbal drug design.

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Authors' contributions

Ichwan Baihaki contributed to the conceptualization of the study, methodology development, microbiological analysis, data interpretation, and manuscript preparation. Khrisna Pangeran contributed to the study design, chemical and pharmacological aspects, data analysis, and critical revision of the manuscript. Herera Rahajeng contributed to pathological interpretation, validation of findings, and manuscript review. All authors contributed to the discussion of results, reviewed the final manuscript, and approved the submitted version.

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None.

Conflict of interest

The authors declare that there are no conflicts of interest related to this work.

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