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In Silico Evaluation of *Bougainvillea*-Derived Phytocompounds as Immunomodulators: Molecular Docking and Simulation Targeting MHC Class I and II Molecules

ANIL KUMAR[1], HOMRAJ SAHARE[2], ANUPAM KUMAR* AND HIMANSHU JANGID[3]

Department of Biotechnology, Faculty of Applied and Health Sciences, Parul University, Goa-403 723 (Goa), India
**(e-mail: anupam.kumar167@gmail.com; Mobile: 98775 20188)*

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ABSTRACT

The present study explored the immunotherapeutic potential of phytochemicals derived from *Bougainvillea* species by targeting Major Histocompatibility Complex (MHC) class I and II receptors. A total of 244 compounds were collected from literature and evaluated through molecular docking using Instadock. Among them, Momordin IIC exhibited the highest binding affinities against both MHC class I (–11.0 kcal/mol) and MHC class II (–9.6 kcal/mol). ADMET simulations conducted with pkCSM tool showed that Momordin IIC was not mutagenic, not hepatotoxic and stable, though its absorption into the intestine was low. The presence of stable complexation, active hydrogen bonding and low structural variations observed in the Momordin IIC-MHC complexes were confirmed by molecular dynamics simulations conducted throughout a 100 -ns trajectory using YASARA. These results indicate that Momordin-IIC has the potential to be used as an effective natural immunomodulator focused on MHC pathways and can be used in immune-based therapy or vaccine development.

Key words: MHC class I, MHC class II, Momordin IIC, *Bougainvillea* species, molecular docking

INTRODUCTION

The immune system's ability to recognize and eliminate pathogens and abnormal cells depends heavily on the antigen-presenting machinery of Major Histocompatibility Complex (MHC) molecules. MHC class I presents endogenous antigens to CD8+ cytotoxic T lymphocytes, while MHC class II displays exogenous peptides to CD4+ helper T cells. These pathways are critical not only in infection control but also in cancer immunity and autoimmune disease management (Dhatchinamoorthy *et al.,* 2021). The therapeutic modulation of MHC-peptide interactions is a growing area of interest in drug discovery, vaccine development and immunotherapy (Buonaguro and Tagliamonte, 2023). Natural compounds, especially those derived from medicinal plants, have emerged as potential immunomodulators due to their structural diversity and biological activity. *Bougainvillea*, a widely distributed ornamental and medicinal plant, is rich in phytochemicals such as flavonoids, alkaloids, phenolics and terpenoids (Mahey *et al*., 2025). These compounds have demonstrated antioxidant, anti-inflammatory, hepatoprotective and antidiabetic properties in previous studies. Notably, compounds like quercetin 3-â-D-glucoside and hesperetin 7-rutinoside isolated from *Bougainvillea* have shown promising binding affinity in molecular docking studies targeting cardiovascular proteins. However, their potential to bind and modulate immune-related receptors such as MHC class I and II has not yet been thoroughly explored. Investigating these interactions could reveal new therapeutic avenues for enhancing immune response or developing plant-based immunomodulatory agents. Therefore, the aim of this study was to perform molecular docking

[1]Department of Botany, School of Bioengineering and Biosciences, Lovely Professional University, Phagwara-144 411 (Punjab), India.
[2]Department of Horticulture, School of Agriculture, Lovely Professional University, Phagwara-144 411 (Panjab), India.
[3]Department of Microbiology, School of Bioengineering and Biosciences, Lovely Professional University, Phagwara-144 411 (Punjab), India.

and molecular dynamics simulations of selected *Bougainvillea*-derived phytocompounds against MHC class I and II molecules (Halder *et al*., 2023). Additionally, *in silico* ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) profiling will be conducted to evaluate the drug-likeness and safety of these compounds (Saritha *et al*., 2024).

MATERIALS AND METHODS

A total of 244 phytochemicals were compiled through an extensive literature review of bioactive constituents (Abarca-Vargas and Petricevich, 2020) from *Bougainvillea* species, a plant species known for its wide-ranging therapeutic activities such as antioxidant, anti-inflammatory and immunomodulatory effects (B. S. and Fauzia, 2021). These compounds include flavonoids, alkaloids, terpenoids, phenolics and glycosides (Makerly and Hashim, 2024). The 2D structures of these compounds were downloaded from the PubChem database in SDF format. Using Open Babel, all compounds were converted to 3D structures and energy minimized with the MMFF94 force field to ensure optimized geometries for molecular docking studies.

All 244 phytochemicals were docked against both MHC class I (PDB ID: 1CE6) and MHC class II (PDB ID: 1SEB) receptors to evaluate their binding potential. The receptor structures were prepared using AutoDock Tools 1.5.6, which involved removal of water molecules and co-crystallized ligands, addition of polar hydrogens and assignment of Gasteiger charges. Docking simulations were performed using InstaDock (Mohammad *et al*., 2021). Grid boxes were set around the known peptide-binding grooves of the MHC molecules. Each compound was docked individually, and binding affinities (in kcal/mol) were recorded. The docked complexes were visualized and analyzed using PyMOL and Discovery Studio Visualizer to investigate interactions such as hydrogen bonds, ð–ð stacking, and hydrophobic contacts with key residues in the binding pocket.

Momordin IIc were further subjected to ADMET analysis using the pkCSM web server Canonical SMILES of all 244 phytochemicals were submitted to predict their absorption, distribution, metabolism, excretion and toxicity profiles. Key parameters assessed included gastrointestinal (GI) absorption, blood brain barrier (BBB) permeability, cytochrome P450 inhibition, hepatotoxicity, total clearance and skin sensitization potential. Each compound was also screened for drug-likeness using Lipinski's Rule of Five. Only compounds with acceptable pharmacokinetic and safety profiles were retained for molecular dynamics simulation.

Molecular dynamics (MD) simulations were conducted for Momordin IIc against MHC I and II complexes to assess the stability and dynamic behaviour of the interactions. Simulations were performed using YASARA (Ozvoldik *et al*., 2023). Structure with the AMBER14 force field. Each ligand–protein complex was solvated in a cubic simulation cell using the TIP3P water model and neutralized with Naz and Cl{ ions. After energy minimization, systems were equilibrated under standard physiological conditions (298 K, 1 atm), followed by a 100-nanosecond production run. Trajectories were analyzed to calculate root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), and hydrogen bond interactions, providing insight into the stability and conformational flexibility of each complex over time.

RESULTS AND DISCUSSION

All 244 phytochemicals collected from *Bougainvillea* species were docked against both MHC class I (PDB ID: 1CE6) and MHC class II (PDB ID: 1SEB) receptors. Binding affinities ranged from moderate to strong, with several compounds showing high docking scores, indicating potential for stable and specific interactions with the antigen-binding grooves of MHC molecules. Table 1 shows top five phytochemicals from *B.* species with highest binding affinities (kcal/mol) against MHC class I and MHC class II receptors. In MHC class I docking, the compound labelled 1CE6_Momordin IIc exhibited the highest binding affinity of –11.0 kcal/mol, followed closely by 1CE6_Alliospiroside C (–10.8 kcal/mol) and 1CE6_Vitisfuran B (–10.2 kcal/mol). Similarly, in MHC class II docking, the compound 1SEB_Alliospiroside C showed the strongest binding at –9.6 kcal/mol, followed by 1SEB_Vitisfuran B (–9.3 kcal/mol) and

Table 1. Top five phytochemicals from *Bougainvillea* with highest binding affinities (kcal/mol) against MHC class I and MHC class II receptors, identified via AutoDock Vina. Momordin IIc showed the strongest binding to MHC I (–11.0 kcal/mol), while Alliospiroside C showed the highest affinity for MHC II (–9.6 kcal/mol)

MHC I		MHC II	
Ligand	Binding affinity	Ligand	Binding affinity
Momordin IIc (14162557)	-11	Alliospiroside C (4638509)	-9.6
Alliospiroside C (4638509)	-10.8	Vitisifuran B(131751783)	-9.3
Vitisifuran B (131751783)	-10.2	1,3,5-Triphenylcyclohexane (119930)	-9.1
Goyaglycoside h (85203191)	-10.1	Momordin IIc (14162557)	-8.9
Robinin (5281693)	-9.7	Goyaglycoside h(85203191)	-8.8

1SEB_1,3,5-Triphenylcyclohexane (–9.1 kcal/mol).

Visual inspection of the top-scoring complexes revealed multiple key interactions stabilizing the ligand receptor binding. Momordin IIc show best stability and binding sites interaction. Fig. 1 (left) shows the 2D interaction profile of 1CE6_Momordin IIc with MHC class I. The ligand forms several conventional hydrogen bonds (green dashed lines) with residues such as ASP A317, TYR A59 and ARG A5, along with ð-alkyl and alkylinteractions with PHE A56, LEU A63 and VAL A28, suggesting a stable and hydrophobic binding environment within the MHC groove. Fig. 1 (Right) illustrates the binding of 1SEB_Momordin IIc with MHC class II. Similar to MHC I, the ligand forms strong hydrogen bonds with THR A34, ASN A35 and GLU A38, in addition to alkyl/ð-alkyl interactions with LEU A37, ALA A39 and PHE A35, indicating favourable hydrophobic and electrostatic interactions. These interactions collectively suggest strong complementarity between the ligands and the antigen-presenting grooves of MHC molecules, contributing to the observed high binding affinities.

The pharmacokinetic and toxicity profile of Momordin IIC a highly performing ligand from molecular dockingof 244 phytochemicals from *B.* species was modeiled using the pkCSM web server. The compound was found to have moderate water solubility (-2.859 log mol/l) and low Caco-2 permeability (-0.908 log Papp),

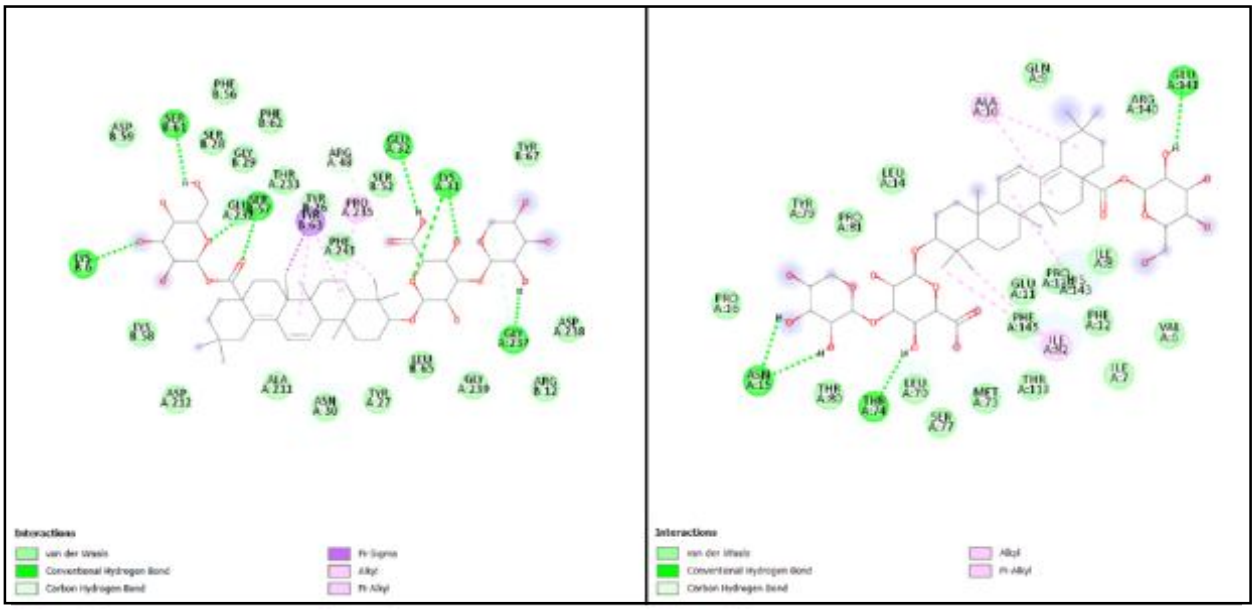

Fig. 1. 2D interaction diagrams of Momordin IIC against phytochemicals docked with MHC receptors. (Left) Momordin IIC interaction with MHC class I showing multiple hydrogen bonds, ð-alkyl, and van der Waals interactions stabilizing the ligand in the binding groove. (Right) Momordin IIc interaction with MHC class II displaying conventional hydrogen bonds and hydrophobic interactions with key residues, indicating strong and specific binding affinity.

which showed poor membrane permeability. The human intestinal absorption was predicted to be 0% indicating low oral bioavailability. It was found to be a P-glycoprotein substrate, but not an inhibitor of P-glycoprotein I or II, suggesting that it might be effluxed without any transporter-related drug-drug interactions. Distribution wise Momordin IIC possessed low volume of distribution (VDss = -0.624 log L / kg) and moderate plasma protein binding (fraction unbound = 0.424). It showed low blood-brain barrier (-2.032 log BB) and CNS permeability (-4.895 log PS), which means that it has little penetration into the central nervous system an attractive quality of a non-CNS-targeted drug. Momordin IIC did not have any predicted substrate or inhibitor of the major cytochrome P450 isoforms (CYP2D6, CYP3A4, CYP1A2, CYP2C19 and CYP2C9) and, therefore, there was low risk of metabolic interactions. The drug had poor total clearance (0.146 log ml / min / kg) and was not an OCT2 renal substrate suggesting the drug could be excreted through non-renal pathways. Toxicological examination showed no mutagenic pattern (negative AMES test) and no anticipated hepatotoxicity or skin sensitization. It also lacks hERG I or II inhibition which means that it is unlikely to cause cardiotoxicity. The predicted acute oral toxicity (LD 50) in rats was 2.596 mol / kg, chronic toxicity (LOAEL) was 4.312 log mg / kg / day, which are both relatively safe. The combination of all these findings forms an indication that Momordin IIC is safe, is metabolically stable and is non-toxic, but has a low absorption rate that can inhibit bioavailability and necessitate formulation / delivery optimization.

In order to determine the dynamic stability of the 1CE6 (MHC class I) with Momordin IIc complex, a 100-nanosecond molecular dynamics (MD) simulation (Fig. 2) was conducted using the YASARA software. The RMSD (Root Mean Square Deviation) plot revealed that the complex was structurally stable after approximately 20 ns and the RMSD values ranged between 2.0-3.5 A at different points of time during the simulation, which is an indicator that the ligand was stable in the receptor pocket. Flexibility in side chains only slightly increased all atom deviation (RMSDAll) yet convergence was achieved. The RMSF (Root Mean Square Fluctuation) plot indicated that the localized fluctuations were mainly in loop areas of the receptor. The residues, which reacted with the ligand, had relatively low value

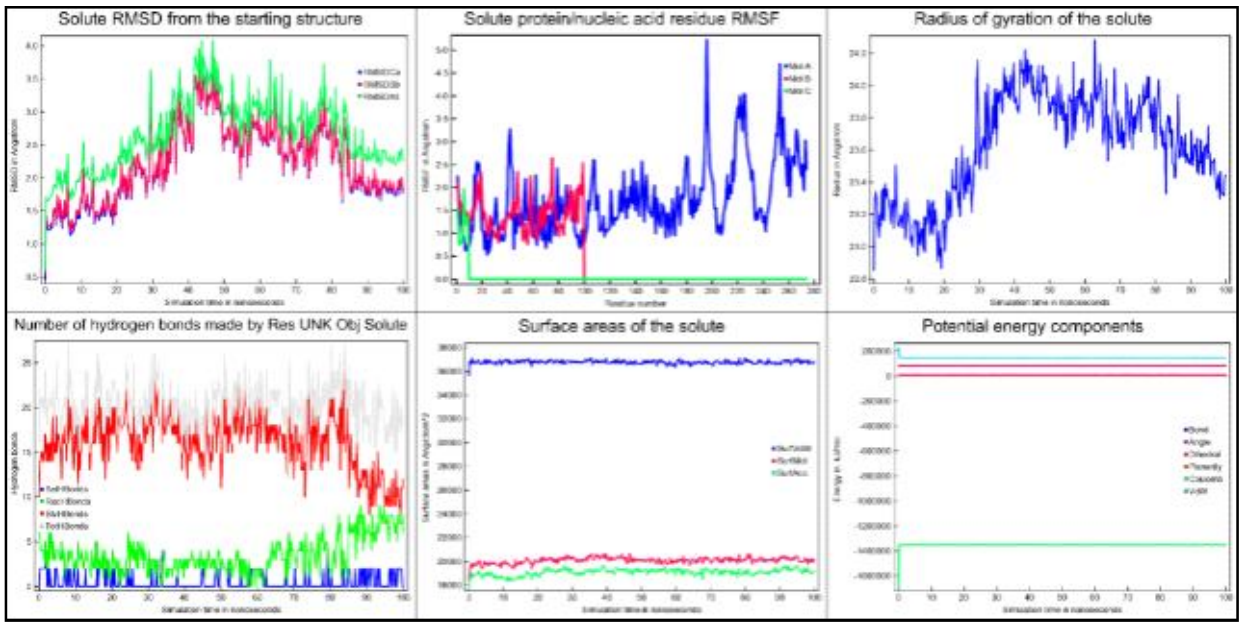

Fig. 2. Molecular dynamics simulation analysis of the Momordin IIC with MHC class I complex over 100 ns. (Top row, left to right): RMSD plot shows structural stabilization after ~20 ns; RMSF plot indicates moderate flexibility in loop regions; Radius of gyration (Rg) confirms stable compactness throughout the simulation. (Bottom row, left to right): Consistent hydrogen bonding observed throughout the trajectory; surface area plots demonstrate no significant conformational collapse; potential energy components remain stable, confirming thermodynamic stability of the complex.

of RMSF (less than 2 A) which indicated that there was minimal flexibility in the interacting residues and established interactions at the attachment site. The radius of gyration (Rg) was varying between 23.2 A and 24.2 A with a slight increase of the simulation between 30-70 ns before becoming stable at the end of the simulation. This indicates that there is a constant compactness of the protein-ligand complex throughout the MD run. The analysis of hydrogen bonding revealed that the count of receptors-ligand hydrogen bonds (RecHBonds) was stable over the course of the trajectory with an average of 10-15 bonds, whereas the total number of hydrogen bonds (TotHBonds) reached its highest point of about 25. This implies that the hydrogen bonding between 1CE6 and MHC class I is strong and persistent over time, which is supported by surface area analysis that showed consistency of values between all measures Van der Waals surface area (SurfVdW), molecular surface area (SurfMol) and solvent-accessible surface area (SurfAcc) showing that the solute was compact throughout the simulation. Lastly the potential energy plot was very stable in all the energy components. The stabilization of the systems was largely due to the contribution of coulombic and Van der Waals (VdW) but bond, angle and dihedral energies were flat, meaning that there was no significant conformational change. The thermodynamic stability of the complex was verified by the system which had a constant potential energy of less than -1,400,000 kJ/mol. To assess the stability of the structural properties and interaction pattern of the 1SEB (MHC class II) Momordin IIc complex (Fig. 3), a 100-nanosecond molecular dynamics (MD) simulation was performed. The RMSD plot revealed a slow rise in deviation in the first half of the simulation to reach 5.0 A at the conclusion of the 100 ns run. This implied that the complex was moderately adjusted in conformational terms and it was then allowed to stabilize. Although a bit greater than that of rigid complexes, the steady trend is a sign of a flexible but stable binding conformation. The RMSF analysis showed that the protein had a significant variation in the N-terminal region of the protein especially below 20 and the highest value was above 12 A. These large variations would be associated with flexible loop regions who are not directly involved in the binding of the ligands. By comparison, there

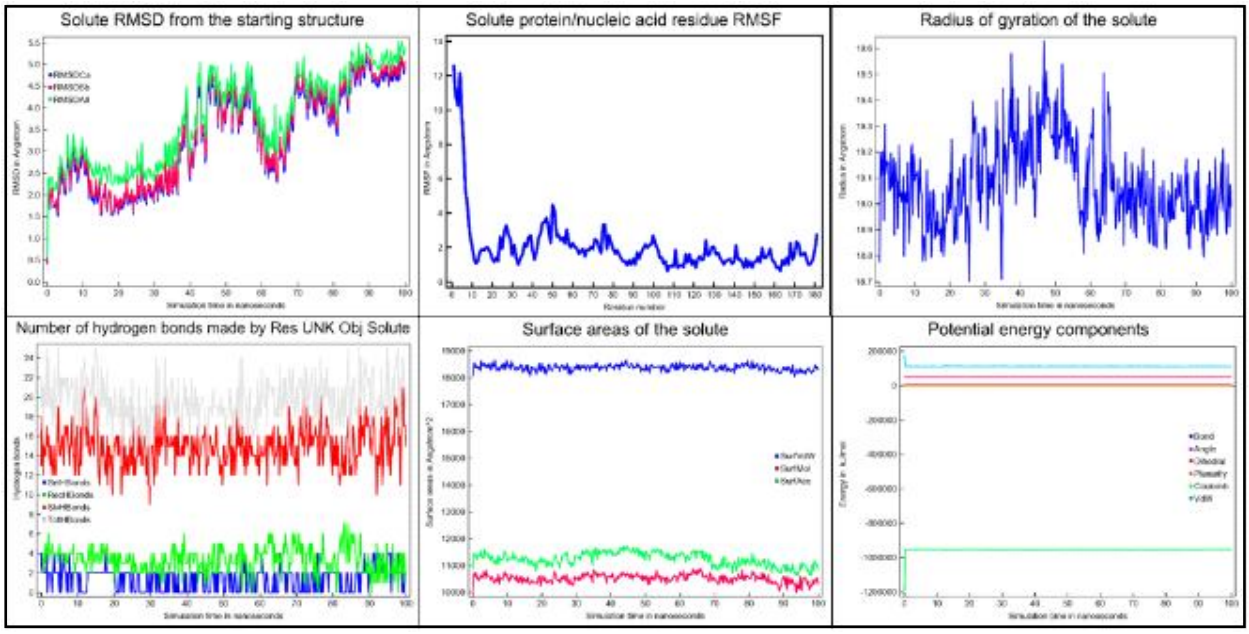

Fig. 3. Molecular dynamics simulation results of the Momordin IIc with MHC class II complex over 100 ns. (Top row, left to right): RMSD plot indicates increasing structural deviation with stabilization toward the end; RMSF plot highlights high flexibility in the N-terminal loop regions; Radius of gyration (Rg) shows moderate fluctuations in complex compactness. (Bottom row, left to right): Stable hydrogen bonding throughout the simulation; surface area metrics remain consistent, suggesting structural integrity; potential energy components are steady, indicating overall thermodynamic stability of the complex.

were far fewer fluctuations in residues of the binding groove, most of which were less than 2 A, indicating a tight and stabilized contact with the ligand. The radius of gyration (Rg) oscillated with values of between 18.8 A and 19.6 A all over the course of the simulation and became unstable between 30-60 ns and stabilized back to normalcy. These values show moderate variations in the compactness of the complex which aligns with the trends in the RMSD. The pattern of hydrogen bond kept constant and receptor hydrogen bonds with the ligands (RecHBonds) formed an average of 12-16 hydrogen bonds and the total hydrogen bonds (TotHBonds) was as high as 24. These interactions play a major role in the total complicated stability. The process of analysis of surface areas showed some consistent trends throughout the simulation. SurfAcc, SurfVdW and SurfMol all were stable with small fluctuations showing that there was no large-scale conformational collapse or unfolding of solute. The elements of potential energy did not change throughout the simulation. The Coulombic and Van der Waals forces were the most significant contributors to the stability of the system, and bond, angle and dihedral forces were flat, which means that the system is not under structural strain. The total potential energy did not change significantly, and it stayed approximately at -1,100,000 kJ/mol, which indicates the thermodynamic favourability of the ligand-receptor complex.

CONCLUSION

This study strictly evaluated immunomodulatory property of 244 phytochemicals found in *Bougainvillea* species through evaluating their interactions with MHC class I and II receptors. Molecular docking identified Momordin IIC as the top-affinity ligand of each of the MHC targets. The stability and persistence of these complexes were supported by longitudinal molecular dynamics simulations over 100 ns. The use of the ADMET profiles that followed, supported the safety profile of Momordin IIC, which showed no signs of toxicity and was metabolically stable, but oral bioavailability was not high. Overall, these findings indicate that Momordin IIC holds strong potential as a natural immunomodulator, warranting further experimental validation for its use in immune-targeted therapies or vaccine adjuvant strategies.

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