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Original Article

Targeting cannabinoid receptor 1 for multiple sclerosis: molecular docking and dynamic insights of berberine and curcumin as potential therapeutic agents

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Abstract: Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system characterized by demyelination, inflammation, and progressive neurodegeneration. Cannabinoid receptor 1 (CB1) plays a role in neuroprotection and modulation of inflammatory responses, making it a potential therapeutic target in MS. This study evaluated selected natural compounds as CB1 modulators using an integrated computational approach. Compounds were screened based on ADMET properties, followed by molecular docking and 100 ns molecular dynamics simulations. Berberine and curcumin demonstrated binding affinities of -7.9 kcal/mol and -9.4 kcal/mol, respectively. Key binding interactions involved residues VAL137, LEU404, PHE408, ARG405, and ARG409 for berberine, and MET363, LEU193, LEU359, TRP356, PHE189, PHE177, HIS178, PHE174, PHE379, ALA380, and SER383 for curcumin. Stability analyzes including RMSD, RMSF, secondary structure elements, and protein-ligand contacts, indicated stable complex formation. These findings suggest that berberine and curcumin may serve as potential lead candidates targeting CB1 and warrant further experimental validation in multiple sclerosis research.

Keywords: Multiple sclerosis, cannabinoid receptor 1 (CB1), molecular docking, molecular dynamics simulations, berberine, curcumin, ADMET analysis, neuroinflammation

Introduction

Multiple sclerosis is a neurological disease of the central nervous system. As it remains for a longer time period, termed a chronic neurological inflammatory disease [1]. It affects one out of thousands of individuals. In the US, the majority of patients affected by multiple sclerosis need assistance while walking within fifteen years of disease progression. Multiple sclerosis affects more than 2.5 million people worldwide. Women ratio is higher than men, and usually adults are affected by multiple sclerosis [2]. The main cause of MS is still unknown, but genetic and non-genetic factors such as environmental effects, viruses, sunshine, and metabolism result in an autoimmune attack on the central nervous system. EBV causes rapid B-cell growth and immortalizes them, and this conversion plays a role in the development of multiple sclerosis. A true EBV-negative person is protected from getting this neurodegenerative disease [3]. Lower vitamin D intake and less outdoor activity can lead to the causal pathway of multiple sclerosis. People with low vitamin D were more likely to get this condition. HLA-DBR *15 serves as a binding site for the EBV virus; it may be identified by HLA genotyping, as it is commonly found in MS patients. More than 150 types of SNPs linked with Multiple Sclerosis liability. Commonly, it is observed that at the start of the disease, the patients will pass from the relapsing- remitting phase of multiple sclerosis [4]. In this phase, symptoms worsen (relapses), followed by recovery (remission). This category is called the Relapsing-Remitting phase of Multiple Sclerosis (RRMS). As the disease progressed, the condition worsened without a relapse-remitting phase, called secondary progressive multiple sclerosis (SPMS). SPMS develop after 10 to 15 years of RRMS [5]. The neurological functioning gets worse and occasionally causes a relapse-remitting condition. With respect to the time

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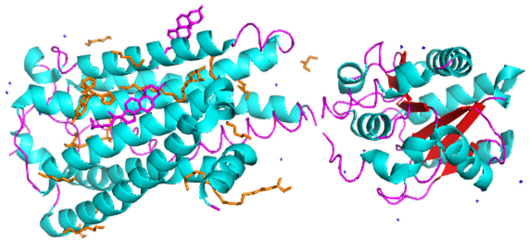


Figure 1. Crystal structure of cannabinoid receptor 1 (CB1) (PDB ID: 7FEE) showing the receptor architecture and ligand-binding region.

period, the symptoms start getting worse, and there is no relapse-remitting condition; this category is called Primary Progressive Multiple Sclerosis (PPMS). Progressive-Relapsing Multiple Sclerosis (PRMS) is the least common category in which the relapse period starts at any point, but no period of remission [6].

The central nervous system comprises the brain and the spinal cord. Oligodendrocytes wrap multiple axons with a myelin membrane to sheath axons. Myelin helps in quick synaptic transmission and also gives metabolic support to axons. Demyelination slows down the transmission of electrical impulses and causes neurodegenerative diseases such as Multiple Sclerosis [7]. Multiple sclerosis is an autoimmune disease in which the immune system attacks the myelin sheath of myelinated axon nerve fibres, causing damage. Demyelination and oligodendrocyte destruction cause inflammation. Initially, the axons remain undamaged, but the disease progression causes damage to the axons, which is irreversible and causes symptoms to worsen [8]. The continuous destruction of the myelin sheath and inflammation play a role in disease progression. The strategy can be applied to treat MS, which could be the control of inflammation that causes myelinated axon damage in the central nervous system. Fingolimod (FTY720) was the first approved drug for the relapse-remitting Multiple Sclerosis. S1P isoforms S1P1, S1P3, S1P4, and S1P5 are the targets for this drug [9]. Cannabinoid receptors involved in pain relief and neuroprotection are considered helpful in MS treatment. Although CB1 involvement in MS and the pharmacological properties of berberine and curcumin have been reported independently, a systematic computational investigation of their binding behaviour, stability profiles, and interaction dynamics with the high-resolution CB1 crystal structure (PDB ID: 7FEE) has not been conducted [10]. The present study provides a side-by-side comparison of these phytochemicals using molecular docking and long-term molecular dynamics, highlighting specific binding residues, interaction persistence, and structural stability within the CB1 active site (**Figure 1**). This comparative structural insight may contribute to rational lead optimization strategies targeting CB1-mediated neuroinflammation.

Cannabinoid receptor 1 comprises only chain "A", having seven different ligands that attach to it. Cannabinoid receptor 1 is a G-protein-coupled receptor for endocannabinoids. The cannabinoid receptors were discovered from 1992 to 1995 [11]. The cannabinoid receptors are located in the hippocampus and also in many peripheral tissues. The specific signalling events activate the cannabinoid receptors. It is involved in regulating the learning process and memory functioning. It is also involved in regulating pain perception and inflammation [12]. Endocannabinoids attach to the CB1 receptor to relief chronic pain and make the cell response to inflammation. It has a variety of applications in psychiatric conditions, like mood regulation and regulating anxiety levels [13]. Abnormal cannabinoid receptors are involved in different diseases, including tumors formation, diabetes, and obesity. It is also involved in autoimmune diseases, including Multiple sclerosis, inflammatory conditions, and rheumatoid arthritis [14].

Materials and methods

Data retrieval and preparation

The crystal structure of cannabinoid receptor 1 has been retrieved from the RCSB Protein Data Bank (PDB) (https://www.rcsb.org/search) and has PDB ID 7FEE [15]. It is classified as a membrane protein determined through the X-ray diffraction method, with a resolution of 2.70 Å. Cannabinoid receptor 1 consists of a single chain A. For accomplishing the task, the target protein was visualized in the PyMol software. PyMol is a graphical application used to animate, visualize and analyze the biomolecules. The 3D visualization of proteins, DNA, RNA, and other small biomolecules provide deep insight

into their morphology. PyMol it was used to remove water molecules and small compounds. The energy minimization of the receptor was done with the aid of the Swiss PDB viewer software. The 3D structures of ligands, including Berberine, Quercetin, Curcumin, and Resveratrol, was retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). These ligands are natural compounds, as natural compounds gain popularity in the treatment of a variety of diseases due to their effective results.

Pharmacokinetics properties prediction

Pharmacokinetics assessment of considering drugs is an essential process to ensure the safety and efficiency. *In silico* approaches provide the facility to validate whether the compounds can become a potential and safe drug for living organisms. The assessment of drug reliability in labs by applying different methods is very costly and time-consuming, but the *in silico* approaches provide the facility to reduce cost and resources by screening a huge number of compounds virtually. After the predictions, the selected compounds are being tested in labs to validate their safety and efficiency. Pharmacokinetics properties prediction reveal the information about the intestinal absorption, distribution, blood-brain barrier, CaCo2 permeability, toxicity, and various physicochemical properties of compounds [16-18]. A variety of software is available for ADMET analysis. PkCSM (https://biosig.lab.uq.edu.au/pkcsm) is a reliable software, and it is publicly available for researchers. To accomplish the determined goal pkCSM [19]. It is utilized to predict the pharmacokinetic properties. The compounds have been eliminated and selected based on the results.

Toxicity analysis

ADMET properties play an essential role in the development of drugs, consumer products, food additives, and chemicals. Toxicity is a major perspective of the failure of drugs during trials. Toxicity evaluation is a significant step in drug development. Absorption, Distribution, Metabolism, Excretion and toxicity characterization, Human intestinal absorption, blood-brain barrier, skin sensitization, hepatotoxicity, aqueous solubility, AMES toxicity, oral rat acute toxicity, oral rat chronic toxicity, drug likeness, mutagenicity, tumorigenicity, irritant and reproductive effects were calculated with the aid of reliable software, including PkCSM and data worrier.

Molecular docking analyzes

Molecular docking is a technique to analyze the interaction, binding affinity, and binding pose between two biomolecules, which leads to the formation of a stable complex [20]. PyRx software based on auto dock vina was utilized to dock determined natural compounds against receptor [21]. During this process the default parameters of software. All the ligands go through the process of energy minimization and charges got applied. The molecular docking was performed by maximizing the grid on the receptor. The docking results show the binding affinity between ligands and the receptor. The interactive residue analysis was done by using UCSF chimera software.

Molecular dynamics simulations

Molecular dynamics simulations are a modern technique to observe the behavior of biomolecules in or atoms virtually [22]. It is used to study biophysical systems by applying specified pressure and temperature to a specified area. After molecular docking, the compounds showing the best binding affinity are simulated using the Desmond package available in the Schrödinger suite [23]. The simulation was run for 100 ns. TIP3P solvent mode selected, and the orthorhombic shape of the box specified with minimal volume for the sake of centralized the protein within the bar. The system neutralizes by adding ions with the default parameter of the Desmond package. The OPLS5e force field was chosen, and 1 atm pressure and 300K temperature were utilized [24]. The results of RMSD, RMSF, SSE, and LP contacts were generated and observed by graphical trajectories. All simulation-derived parameters, including RMSD and RMSF were analyzed using Desmond trajectory analysis tools. Stability was evaluated based on the consistency of plateau formation and fluctuation range over 100 ns. Descriptive statistical evaluation of trajectory averages was performed; no inferential statistical tests were applied as the study is computational in nature.

Statistical analysis

All computational data generated from ADMET prediction, molecular docking, and molecular

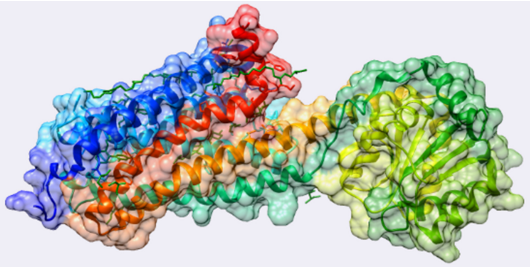


Figure 2. Three-dimensional structure of cannabinoid receptor 1 (CB1), chain A (PDB ID: 7FEE), visualized for structure preparation prior to docking and molecular dynamics simulations.

dynamics simulations were analyzed using descriptive statistical approaches. ADMET and toxicity parameters obtained from pkCSM were tabulated and compared among the selected phytochemicals to evaluate drug-likeness, absorption, distribution, toxicity risk, and pharmacokinetic suitability. Molecular docking results were assessed based on binding affinity values expressed in kcal/mol, where lower binding energy indicated stronger predicted ligand-receptor interaction. The docking poses and interacting amino acid residues were further examined qualitatively using UCSF Chimera. For molecular dynamics simulations, trajectory-based analyses were performed over a 100 ns simulation period using the Desmond simulation interaction analysis tools. Root mean square deviation (RMSD) was used to evaluate the structural stability and equilibration behavior of the protein-ligand complexes throughout the simulation. Root mean square fluctuation (RMSF) was analyzed to determine residue-wise flexibility and local conformational fluctuations. Secondary structure element analysis was performed to assess the stability of α-helices and β-strands during the simulation period. Protein-ligand contact analysis was used to evaluate the type, duration, and persistence of interactions, including hydrophobic interactions, hydrogen bonds, ionic interactions, and water bridges. The simulation results were interpreted based on trajectory stability, fluctuation pattern, interaction persistence, and maintenance of secondary structure over time. Descriptive values such as average trends, fluctuation ranges, and percentage of interaction persistence were considered where applicable. No inferential statistical tests, such as t-tests or analysis of variance, were applied because the present study was entirely computational and did not include experimental biological replicates or independently repeated treatment groups. The results were therefore analyzed descriptively to support comparative interpretation of ligand binding stability and interaction behavior.

Result

Data retrieval

The aim of the current research is to virtually screen the potential compounds for the treatment of multiple sclerosis. The screening involves designing, analyzing, and evaluating determined compounds to find the potential ones for the treatment. The 3D structure of the Cannabinoid receptor 1, with PDB ID 7FEE, was retrieved from the RCSB Protein Data Bank (**Figure 2**). Interestingly, seven different ligands were observed to be attached to the receptor protein. The ligand structures, including Berberine (CID: 2353), Resveratrol (CID_445154), and Quercetin (CID: 5280343), were retrieved from the PubChem database in SDF format.

ADMET analysis

Pharmacokinetic studies reveal information on the drug's safety and efficacy. The failure of the drug to launch in the market is due to its inefficiency and safety issues. The Lipinski rule of five is the standard criterion for passing out of drugs. If the compounds do not pass the required level, then their absorption will be low in the intestine. All the important factors, including Absorption, Distribution, Metabolism, Excretion and toxicity characterization, Human intestinal absorption, blood-brain barrier, skin sensitization, hepatotoxicity, aqueous solubility, AMES toxicity, oral rat acute toxicity, oral rat chronic toxicity, drug likeness, mutagenicity, tumorigenecity, irritant and reproductive effects related to safety and efficiency, were kept under consideration. The predicted ADMET and toxicity profiles of berberine and curcumin are summarized in **Table 1**.

Molecular docking analysis

Molecular docking was performed to evaluate the ligand-receptor binding affinity. The results show the binding interaction, binding energy, and binding pose of the ligand with the receptor. The following results show the binding aff-

Table 1. ADMET and toxicity analysis of compounds

Features	Berberine	Resveratrol	Quercetin	Curcumin
CID	2353	445154	5280343	969516
Molecular Weight	336.367	228.247	302.238	368.385
Rotatable Bonds	2	2	1	8
H-Bond Acceptors	4	3	7	6
H-Bond Donors	0	3	5	2
Intestinal Absorption (%)	97.147	90.935	77.207	82.19
BBB Permeability	0.198	-0.048	-1.098	-0.562
LogP	3.0963	2.9738	1.988	3.3699
cLogS	-4.669	-2.864	-2.491	-3.622
Caco2 Permeability	1.734	1.17	-0.229	-0.093
Skin Sensitisation	NO	NO	NO	NO
Hepatotoxicity	NO	No	No	No
Ames Toxicity	NO	NO	No	No
Oral Rat Acute Toxicity	2.571	2.529	2.471	1.833
Oral Rat Chronic Toxicity	1.89	1.533	2.612	2.228
Druglikeness	-2.2467	-1.6732	-0.0828	-4.7745
Mutagenic	None	High	High	None
Tumorigenic	None	None	High	None
Reproductive Effect	None	High	None	None
Irritant	None	None	None	None

inities of the respective ligands with cannabinoid receptor 1. The molecular docking scores of all screened compounds against cannabinoid receptor 1 (CB1) are presented in **Table 2**. Based on ADMET analysis and molecular docking, berberine and curcumin were identified as potential compounds that can ensure safety and efficiency.

The interaction between ligands and protein residues was observed with the aid of the UCSF Chimera tool. The specific compounds that show the best binding energy and pass the ADMET criteria were visualized in the tool to analyze the interactive residues (**Figure 3**). The interactive residues of protein with Berberine (CID_2353) are VAL137, LEU404, PHE408, ARG405, and ARG409. The interactive residues of protein with Curcumin (CID_969516) are MET363, LEU193, LEU359, TRP356, PHE189, PHE177, HIS178, PHE174, PHE379, ALA380, and SER383 (**Figure 4**).

Molecular dynamics simulations analysis

The graphical analysis shows the deviation and fluctuations of biomolecules over time. The molecular dynamics simulations reveal information about the protein's equilibrium and the interaction between the protein and the ligand in the complex. For the purpose of analyzing the stability of the protein, the molecular dynamics simulation and post-docking analysis were done. The complex of 7FEE-Berberine and 7FEE-Curcumin was under consideration because it passed ADMET analysis and showed the lowest binding affinity in the molecular docking results.

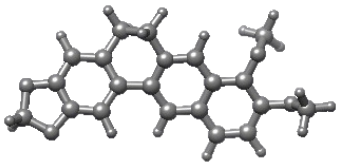
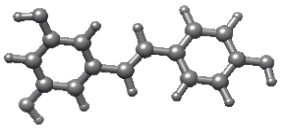
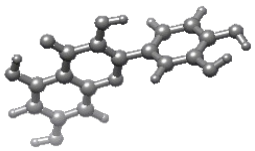
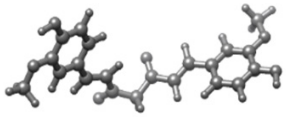
RMSD analysis

The average motion of an atom from its initial location to a reference with respect to a time interval was calculated by Root Mean Square Deviation (RMSD). For the purpose of analyzing the stability of the protein complex, RSMD analysis was done. The changes in the graph show the conformational changes of the protein and ligand over the simulation time period. At 30 ns, the 7FEE-Berberine complex is stable; thereafter, it shows some fluctuations due to secondary structure, and at 40 ns it regains stability and exhibits interaction between the ligand and the protein. The complex of 7FEE-Berberine also remains approximately stable during the molecular dynamics simulation. 7FEE- Berberine complex deviates initially but gains equilibrium till 50 ns (**Figure 5**). After 50 ns, it deviates more and then becomes stable again until the end. The small deviation for small globular proteins is acceptable, but the larger changes show higher deviation.

RSMF analysis

The RMSF analysis of curcumin and Berberine is done to observe the fluctuation of protein. The peaks in the respective graph show the fluctuating area of protein during molecular dynamics simulations. The root-mean-square fluctuation was observed when the small molecules, including Berberine and curcumin, attached to the protein. The relative RMSD of ligand and protein shows that the ligands are

Table 2. Representation of docking score with respect to the mentioned compound names

PubChem CID	Compound name	3D structure	Docking score (Kcal/mol)
CID_2353	Berberine		-7.9
CID_445154	Resveratrol		-8.5
CID_5280343	Quercetin		-9.9
CID_969516	Curcumin		-9.4

diffused in the binding pocket of the protein. The selected compound's RMSF (**Figure 6**) peaks show the maximum fluctuations.

Secondary structure analysis

The percentage of secondary structure in the Cannabinoid receptor 1 is simulated throughout the molecular dynamics simulation. The visualization depiction of secondary structures distribution throughout the structure complexed with Berberine and Curcumin, respectively (**Figure 7**). The total secondary structure of the protein is 53.57%. Alpha helices comprise 48.04% and beta strands comprise 5.53% of the protein structure complexed with Berberine. The total secondary structure of the protein is 54.24%. Alpha helices comprise 48.53% and beta strands comprise 5.72% of the protein structure complexed with Curcumin. Secondary structure analysis is necessary to visualize the protein secondary structure conformation and protein contacts during the simulation process.

Protein ligand contacts

The interaction between cannabinoid receptor 1 and berberine, analyzed with the help of a Protein ligand contacts plot, is shown in **Figure 8A**. The analysis shows the interaction types, including hydrogen bonds, hydrophobic interactions, ionic interactions, and water bridges. The unique interaction was maintained throughout the simulation. The interactive residues of protein with berberine are shown in **Figure 8A**. The graph shows that PHE_408 exhibits stable hydrophobic interactions throughout the simulation period. LEU-399 shows the hydrophobic interaction initially, but after sometime the interaction changed into water bridges (**Figure 8A**).

The interactive residues of protein with curcumin are shown in **Figure 8A**. PHE-170, PHE-174, VAL-196, PHE-268, TRP-356, LEU-359, and PHE-379 exhibit stable hydrophobic interactions over a relatively long period. The remaining residue interaction remained stable for some time but exhibited changes over the period, as shown in **Figure 8B**.

Discussion

Multiple sclerosis is a serious health concern; it is observed that MS is more common in young adults. Multiple sclerosis is a neurodegenerative autoimmune disease in which the body attacks itself. The myelin sheath of myelinated axons was damaged, and synaptic transmission was affected severely. It can be due to genetic issues or environmental factors [25]. If the disease progresses, the continuous dete-

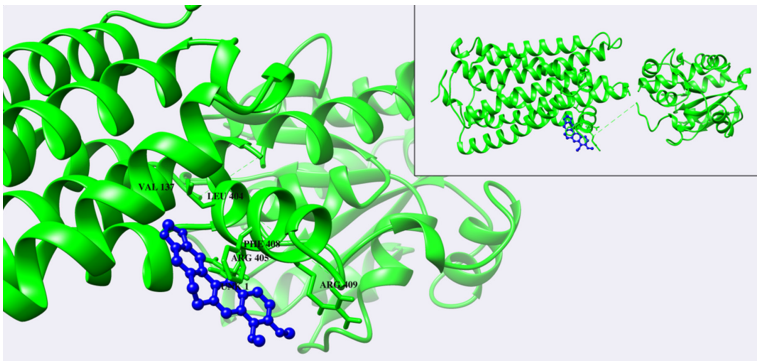


Figure 3. Binding pose of berberine within the CB1 active site (PDB ID: 7FEE) showing key interacting residues visualized in UCSF Chimera.

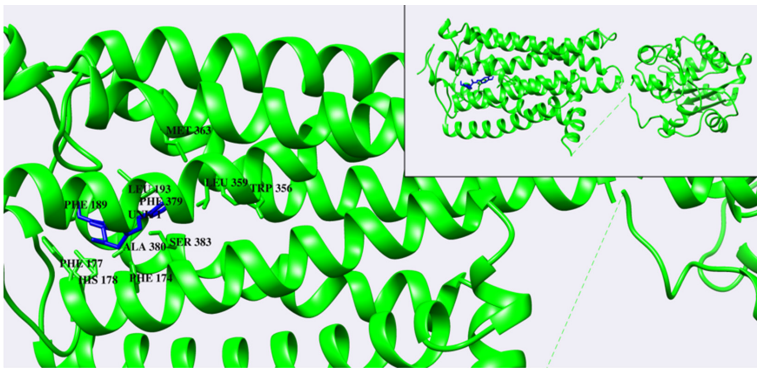


Figure 4. Cannabinoid Receptor 1 complexed with curcumin. The image shows the receptor's interactive residues with curcumin.

rioration of the neurological system causes severe symptoms. Multiple therapies are available to control the disease at different levels, but it is still arduous to control. Multiple sclerosis can cause fatigue, depression, anxiety, loss of vision, numbness, and muscle stiffness [32]. Multiple therapeutic approaches aid in treating it by reducing inflammation, providing neuroprotection, and reducing pain [26]. Cannabinoid receptors are present in the central nervous system. CB1 signaling in multiple sclerosis is complex and context-dependent. While CB1 activation may reduce neuroinflammation and pain perception, excessive modulation can influence cognitive function, mood regulation, and central nervous system excitability. Therefore, therapeutic targeting of CB1 requires careful consideration of receptor distribution, downstream signaling bias, and potential off-target neurological effects [27]. Endocannabinoids bind to receptors and play various roles, including pain reduction.

A pharmacokinetics assessment was conducted to ensure health safety [33]. The Lipinski rule of five stated the criteria that the Molecular weight of a compound should be <500 g/mol, the rotatable bond should be greater than 10, the hydrogen bond donor should be less than five, the hydrogen bond acceptor should be greater than five, and the compounds with those characteristics will be acceptable for oral administration [20]. LogS value of the specific compound determines its solubility within the body [20]. LogP value related to the absorption of the drug [20]. The ability of compounds to harm a living organism's body is referred to as toxicity [34]. Each type of toxicity determination is necessary, depending on the treatment of its affected sites within the body. Mutagenicity, tumorigenicity, irritating effects, reproductive effects, AMES toxicity, oral rat chronic toxicity, oral rat acute toxicity, skin sensitivity, and hepatotoxicity were determined [34]. There are two compounds, Berberine (CID_2353) and Curcumin (CID_969516), that could become valuable drugs after wet-lab analysis.

Understanding the mechanism of interaction between two molecules was a big challenge, but now the molecular dynamics simulation is a promising approach for observing the behavior of proteins, ligands, and other biomolecules [28]. It is used to analyze the stability of a protein in a real-time environment when interacting with ligands. It gives large amounts of data to analyze behavior of atoms [29]. The graphical representation and trajectories make it easy to understand equilibrium, secondary structure elements, interactions, and more. The present work is designed as a hypothesis-generating computational investigation. Experimental validation, such as receptor binding assays, cAMP signaling studies, or neuroinflam-

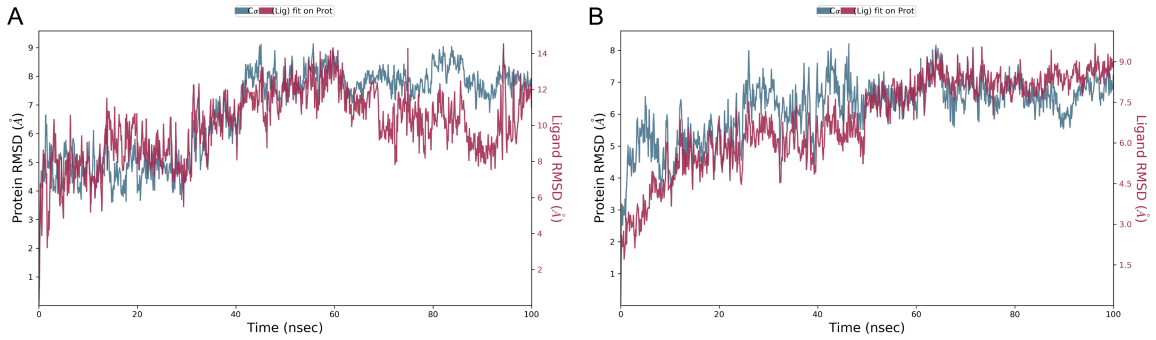


Figure 5. A: RMSD analysis of 7FEE-Berberine complex. B: RMSD analysis of 7FEE-Curcumin complex.

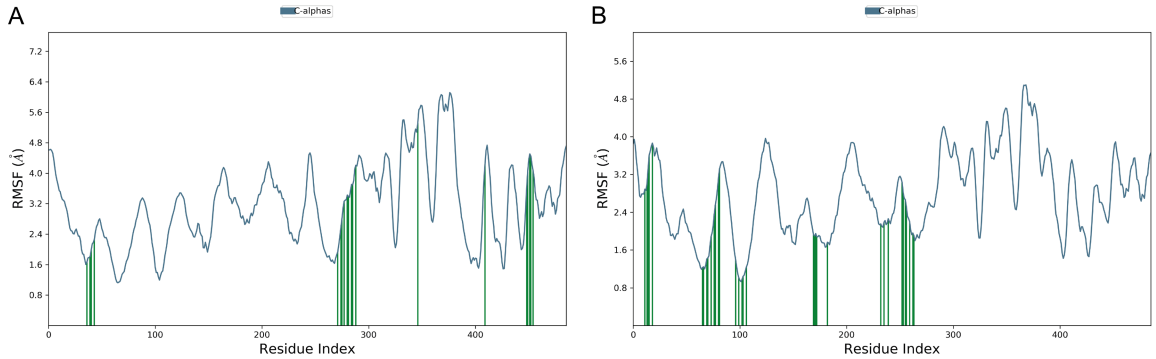


Figure 6. A: RMSF analysis of 7FEE-Berberine complex. B: RMSF analysis of 7FEE-Curcumin complex.

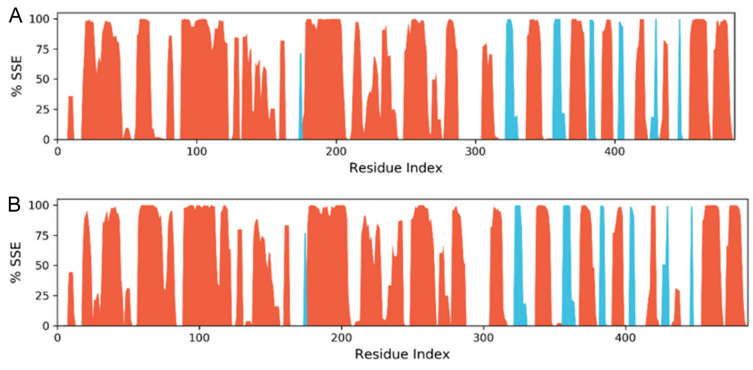


Figure 7. A: The SSE plot of cannabinoid receptor 1 complex with Berberine. B: The SSE plot of cannabinoid receptor 1 complex with Curcumin.

matory cell-based models, was beyond the scope of this study but will be necessary to confirm the predicted receptor interactions and biological relevance [30].

Berberine (CID_2353) and Curcumin (CID_969516) complexed with Cannabinoid Receptor 1 were observed during the simulation time period. Both structures showed minor fluctuations and deviations at different points, but remained stable over a longer time period in RMSD and RMSF analyzes. Secondary structures showed a maximum stability behavior during 100 ns of molecular dynamics simulations [31]. The protein-ligand contact analysis showed the strongest and most stable hydrophobic interaction between Berberine and the 7FEE protein. PHE-408 exhibited hydrophobic interactions and remained stable throughout the entire time period. The interaction between Cannabinoid receptor 1 and Curcumin is determined by the many residues that contact the ligand. PHE-170, PHE-174, VAL-196, PHE-268, TRP-356, LEU-359, and PHE-379 showed stable interactions over a longer period. Based on all necessary analyses, including ADMET, Molecular Docking, residual interactions, and Molecular Dynamics Simulations, it is reported that the interaction of Cannabinoid Receptor 1 complexed with

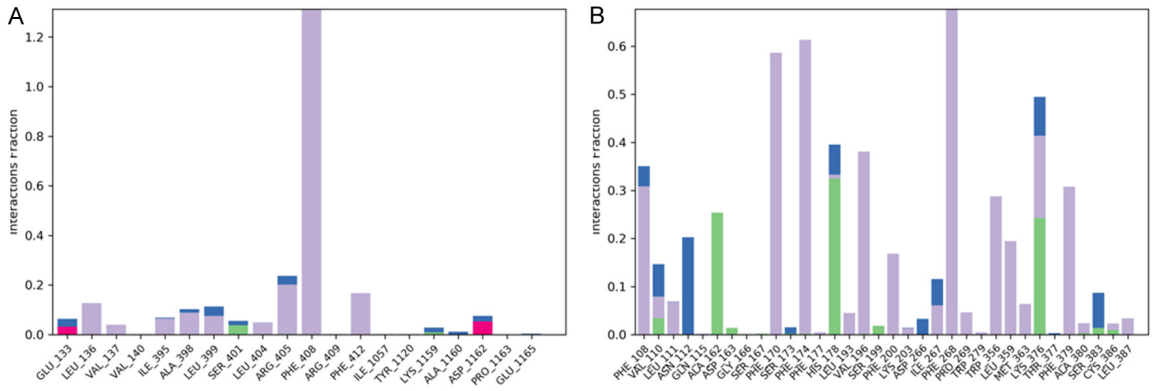


Figure 8. A: The interaction analysis between 7FEE and Berberine. B: The interaction analysis between 7FEE and Curcumin.

Berberine and Cannabinoid Receptor 1 complexed with Curcumin may be helpful for treatment. Berberine and curcumin demonstrated promising computational binding stability and interaction persistence with CB1, suggesting their potential as lead scaffolds for further in vitro and in vivo investigations.

Conclusion

This study computationally evaluated selected natural compounds against CB1 using molecular docking, ADMET profiling, and molecular dynamics simulations. Berberine and curcumin exhibited stable binding conformations and acceptable pharmacokinetic predictions. However, these findings are predictive in nature and require experimental validation to confirm receptor modulation, biological activity, and safety in relevant cellular and animal models.

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Disclosure of conflict of interest

None.

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References

[1] Boutitah-Benyaich I, Eixarch H, Villacieros-Álvarez J, Hervera A, Cobo-Calvo Á, Montalban X and Espejo C. Multiple sclerosis: molecular pathogenesis and therapeutic intervention. Signal Transduct Target Ther 2025; 10: 324.

[2] Marrie RA, Elliott L, Marriott J, Cossoy M, Blanchard J, Leung S and Yu N. Effect of comorbidity on mortality in multiple sclerosis. Neurology 2015; 85: 240-247.

[3] Rasheed A and Khan G. Epstein-Barr virus, vitamin D and the immune response: connections with consequences for multiple sclerosis. Front Immunol 2024; 15: 1503808.

[4] Carlberg C and Mycko MP. Linking mechanisms of vitamin D signaling with multiple sclerosis. Cells 2023; 12: 2391.

[5] Albelo-Martínez M and Rizvi S. Progressive multiple sclerosis: evaluating current therapies and exploring future treatment strategies. Neurotherapeutics 2025; 22: e00601.

[6] McKay KA, Kwan V, Duggan T and Tremlett H. Risk factors associated with the onset of relapsing-remitting and primary progressive multiple sclerosis: a systematic review. Biomed Res Int 2015; 2015: 817238.

[7] Stadelmann C, Timmler S, Barrantes-Freer A and Simons M. Myelin in the central nervous system: structure, function, and pathology. Physiol Rev 2019; 99: 1381-1431.

[8] Understanding Multiple Sclerosis|Brain Institute|OHSU. https://www.ohsu.edu/brain-institute/understanding-multiple-sclerosis.

[9] Podbielska M, Banik NL, Kurowska E and Hogan EL. Myelin recovery in multiple sclerosis: the challenge of remyelination. Brain Sci 2013; 3: 1282-1324.

[10] Martínez-Pinilla E, Calatayud-Morán JM, Menéndez-Pérez C, Villar-Conde S, Rivas-Santisteban R, Peláez R, Navarro A and Franco R. Neu-

roprotective role of cannabinoid CB1 and GPR55 receptors in a cell model of multiple sclerosis. Mol Neurobiol 2026; 63: 482.
[11] Reggio PH. Endocannabinoid binding to the cannabinoid receptors: what is known and what remains unknown. Curr Med Chem 2010; 17: 1468-1486.
[12] Kendall DA and Yudowski GA. Cannabinoid receptors in the central nervous system: their signaling and roles in disease. Front Cell Neurosci 2017; 10: 294.
[13] Șerban M, Toader C and Covache-Busuioc RA. The endocannabinoid system in human disease: molecular signaling, receptor pharmacology, and therapeutic innovation. Int J Mol Sci 2025; 26: 11132.
[14] Nouh RA, Kamal A and Abdelnaser A. Cannabinoids and multiple sclerosis: a critical analysis of therapeutic potentials and safety concerns. Pharmaceutics 2023; 15: 1151.
[15] Yang X, Wang X, Xu Z, Wu C, Zhou Y, Wang Y, Lin G, Li K, Wu M, Xia A, Liu J, Cheng L, Zou J, Yan W, Shao Z and Yang S. Molecular mechanism of allosteric modulation for the cannabinoid receptor CB1. Nat Chem Biol 2022; 18: 831-840.
[16] Du BX, Xu Y, Yiu SM, Yu H and Shi JY. ADMET property prediction via multi-task graph learning under adaptive auxiliary task selection. iScience 2023; 26: 108285.
[17] Dulsat J, López-Nieto B, Estrada-Tejedor R and Borrell JI. Evaluation of free online ADMET tools for academic or small biotech environments. Molecules 2023; 28: 776.
[18] Azmal M, Hossen MS, Shohan MNH, Taqui R, Malik A and Ghosh A. A computational approach to identify phytochemicals as potential inhibitor of acetylcholinesterase: molecular docking, ADME profiling and molecular dynamics simulations. PLoS One 2024; 19: e0304490.
[19] Pires DE, Blundell TL and Ascher DB. pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. J Med Chem 2015; 58: 4066-4072.
[20] Bhutadiya VL and Mistry KN. Virtual screening and molecular docking for the identification of potential antibreast cancer agents targeting estrogen receptor. In: Kaneria M, Rakholiya K, Egbuna C, editors. Nanotechnology and In Silico Tools. Elsevier; 2024. pp. 319-329.
[21] Kondapuram SK, Sarvagalla S and Coumar MS. Docking-based virtual screening using PyRx tool: autophagy target Vps34 as a case study. In: Coumar MS, editor. Molecular Docking for Computer-Aided Drug Design. Academic Press; 2021. pp. 463-477.
[22] Huang J, Rauscher S, Nawrocki G, Ran T, Feig M, de Groot BL, Grubmüller H and MacKerell AD Jr. CHARMM36m: an improved force field for folded and intrinsically disordered proteins. Nat Methods 2017; 14: 71-73.
[23] Huang J and MacKerell AD Jr. CHARMM36 all-atom additive protein force field: validation based on comparison to NMR data. J Comput Chem 2013; 34: 2135-2145.
[24] Jorgensen WL, Maxwell DS and Tirado-Rives J. Development and testing of the OPLS all-atom force field on conformational energetics and properties of organic liquids. J Am Chem Soc 1996; 118: 11225-11236.
[25] Trapp BD and Nave KA. Multiple sclerosis: an immune or neurodegenerative disorder? Annu Rev Neurosci 2008; 31: 247-269.
[26] Arachchige ASPM, El Choueiri J, Pellicanò F, Laurelli F, Alves GAM and Stomeo N. A review of multiple sclerosis: from pathophysiology to latest therapeutic advances. AIMS Neurosci 2025; 12: 514-538.
[27] Manzanares J, Julian M and Carrascosa A. Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes. Curr Neuropharmacol 2006; 4: 239-257.
[28] Hollingsworth SA and Dror RO. Molecular dynamics simulation for all. Neuron 2018; 99: 1129-1143.
[29] Vallejo DD, Rojas Ramírez C, Parson KF, Han Y, Gadkari VV and Ruotolo BT. Mass spectrometry methods for measuring protein stability. Chem Rev 2022; 122: 7690-7719.
[30] Posters. FEBS Open Bio 2025; 15 Suppl 2: 67-527.
[31] Kumar Verma A, Kumar V, Singh S, Goswami BC, Camps I, Sekar A, Yoon S and Lee KW. Repurposing potential of Ayurvedic medicinal plants derived active principles against SARS-CoV-2 associated target proteins revealed by molecular docking, molecular dynamics and MM-PBSA studies. Biomed Pharmacother 2021; 137: 111356.
[32] Kos D, Kerckhofs E, Nagels G, D'hooghe MB and Ilsbroukx S. Origin of fatigue in multiple sclerosis: review of the literature. Neurorehabil Neural Repair 2008; 22: 91-100.
[33] Hedaya MA. Basic pharmacokinetics. 2023: Routledge.
[34] Buist H, Aldenberg T, Batke M, Escher S, Klein Entink R, Kühne R, Marquart H, Pauné E, Rorije E, Schüürmann G and Kroese D. The OSIRIS Weight of Evidence approach: ITS mutagenicity and ITS carcinogenicity. Regul Toxicol Pharmacol 2013; 67: 170-181.