Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 3 Issue 9 September 2019

Research Article

# Computational Characterization of the Binding Energy and Interactions between CB1 Receptor and Its Classical Agonist and Negative Allosteric Modulators (NAMs)

**S Shabber, U Habib* and M Rafiq**

*Department of Computational Sciences, Research Center for Modeling and Simulation NUST, Pakistan*

***Corresponding Author:** U Habib, Department of Computational Sciences, Research Center for Modeling and Simulation NUST, Pakistan.

**Received:** July 26, 2019; **Published:** August 08, 2019

## Abstract

Recent studies have linked modulatory function of the cannabinoid signaling system, namely the role of CB1 receptor in the basal ganglia to the progression of numerous neurological and movement diseases including Parkinson's, Huntington's diseases, Tourette's syndrome, dystonia's, epilepsy, and Alzheimer's. Hence, use of classical cannabinoids as the new therapeutic agents for most neurological and movement seems quite promising. Computational characterization of the binding energy and interactions between CB1 receptor and classical cannabinoids such as Δ9-tetrahydrocannabinol (THC) (a CB1 receptor agonist) and Cannabidiol (CBD) (a CB1 receptor Negative Allosteric Modulators) was conducted using Molecular Operating Environment (MOE). The interactions are hydrogen bonding, aromatic and steric interactions. The best binding energy between THC and CB1 receptor in its active and inactive conformation were -7.6 Kcal/mol and -8.9 Kcal/mol respectively. For CBD and CB1 receptor, the best binding in its active and inactive conformation were -7.9Kcal/mol and -11.3 Kcal/Mol respectively. The negative values of the binding energies showed that the interactions were quite favorable.

**Keywords:** CB1 Cannabinoid Receptor; Δ9-tetrahydrocannabinol (THC); Cannabidiol (CBD); Molecular Docking; Binding Energy; Neurological Disorders

## Introduction

Cannabinoid receptor also known as CB1 receptor belongs to class A G-protein coupled receptors (GPCRs) that represent the largest membrane protein. CB1 receptor is a therapeutically useful target involved in a wide variety of physiological processes, including metabolic regulation, craving, pain and anxiety which are often symptomatic to many neurological disorders. Drugs targeting CB1 receptor are continually being developed as CB1 receptor is one of the most important therapeutic drug targets in most neurological disorders such as Parkinson's and Huntington's diseases. The CB1 receptors are worth considering the abundance of cannabinoid receptors in the brain. All known CB1 ligands are highly diverse structurally and can range from agonists such as Δ9-tetrahydrocannabinol (THC) to positive or negative allosteric modulators [PAMs/NAMs]. One such negative allosteric modulator is the non-psychoactive phyto- cannabinoid cannabidiol (CBD). Hence the CB1 receptor has to undergo considerable conformational changes to accept different ligands, making molecular docking for CB1 challenging [1-3].

It is well documented that in nearly all neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PA), and Huntington's disease (HD), to name a few, share few common feature such as neuronal loss, oxidative stress and neuro- inflammation, which can contribute to the disease symptomatology. Although these diseases differ in etiology the neuro-inflammation

and neuronal loss are the forerunners. The cannabinoid system can impact on these symptoms as major alterations are reported in diseased state to the cannabinoid system and cannabinoid based treatment provides reversal of certain neurodegenerative events. There are four types of cannabinoid agonist: endogenous (body's own), classical (plant based), non- classical (synthetic) and amino-alkylindoles. Plant based cannabinoids despite their controversial stature are being investigated for medical purposed more so every day, as cannabinoids offer treatment for degenerative, inflammatory disorders of the Central nervous system (CNS) [2,4-6].

Insufficient data regarding effectiveness of THC and CBD for seizure disorders is due to the lack of well-designed studies. However, most states where marijuana has been legalized a study proved CBD effective against Dravet syndrome, Lennox-Gastaut syndrome, and neonatal hypoxic- ischemic encephalopathy, which are all seizure related disorders. It has also been reported that THC can treat the central pain and painful spasms caused by multiple sclerosis. One of the persistently faced problems in drug design has always been the discovery of bioactive conformation of a molecule. A conformation that fits with its target-binding site and triggers a biological response, hence in this research article docking studies were performed for CBD and THC to find out the best possible binding pose so that all the reported symptomatic relief reported for neurological and movement related diseases would have scientific ground [7-9].

As far as the computational advancement, when it comes to understanding how cannabinoids and the cannabinoid system namely CB1-receptor-mediated transmission within the basal ganglia, little work has been done in understanding the exact mechanism by which cannabinoid agonist activate the CB1 and CB2 receptors which help protect against neuronal loss, oxidative stress and neuro-inflammation. Many homology model studies of CB1 receptor against ligands are available but there is little to no work showing binding energy and interaction pattern of classic plant based cannabinoids such as CBD and THC to cannabinoid receptors CB1 and CB2 respectively. Understanding the interaction pattern of these psychoactive ligands can help us understand what important interactions are responsible for helping reduce the symptoms of the neurological and movement related diseases under consideration.

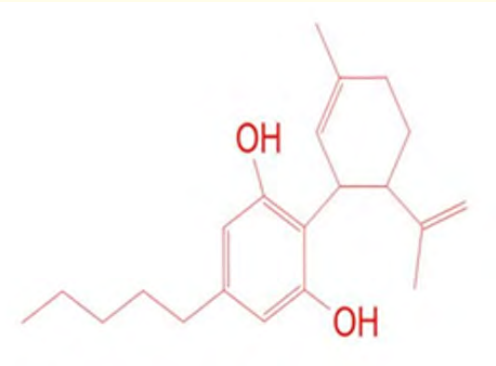


**Figure 1:** 2D structure of cannabidiol (CBD) as depicted in the software MOE.

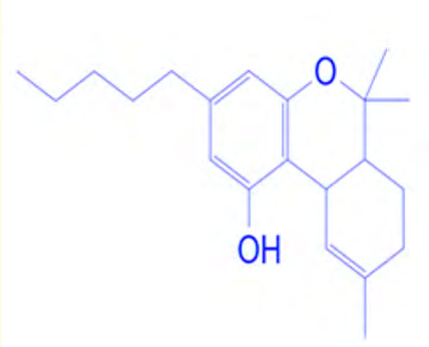


**Figure 2:** 2D structure of Δ9- tetrahydrocannabinol (THC) as depicted in the software MOE.

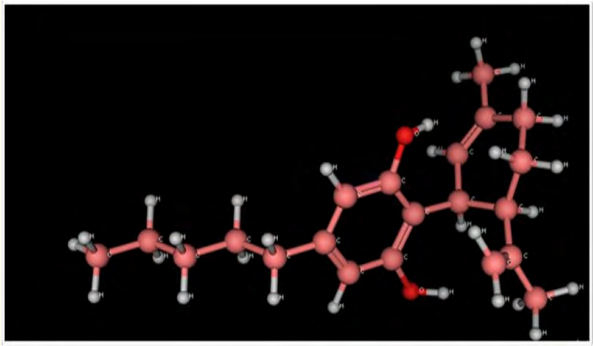

**Figure 3:** 3D structure of cannabidiol (CBD) as depicted in the software MOE.

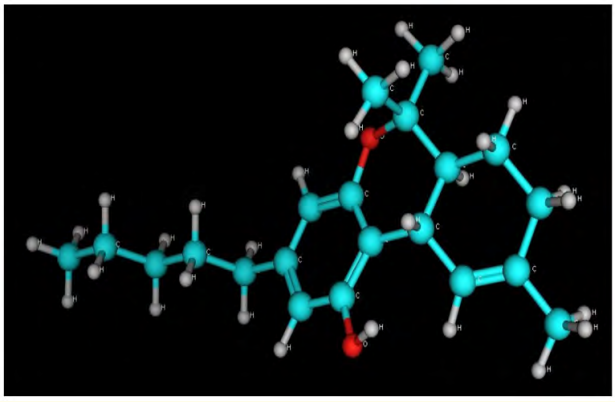

**Figure 4:** 3D structure of Δ9-tetrahydrocannabinol (THC) as depicted in the software MOE.

This work is aimed at studying the computational characterization of the binding energy and interactions between CB1 receptor and its classical agonist and negative allosteric modulators (NAMS). In this article, an agonist of CB1 receptor known as Δ9- tetrahydrocannabinol (THC) and a negative allosteric modulator (NAM) known as cannabidiol (CBD) are used for molecular docking.

## Materials and Methods

### Protein preparation

The crystal structures of the active and inactive conformations of the Cannabinoid receptor CB1, were obtained from the protein data bank (PDB), having the entry number PDB ID: 5TGZ (inactive)10 and 5XRA (active)11 respectively. The reported organisms for both active and inactive conformation of the protein was homo sapiens. The protein structures were prepared for docking using Molecular Operating Environment (MOE) software. Now the protein crystal structures (individually) were imported into the MOE software and edited to remove all water molecules along with any pre-attached ligands. The tautomeric states of residues were adjusted via protonation for which the pH was kept at 7.0, temperature was maintained at 300K and the salt (ionic) concentration retained at 0.1 mol/L (according to the Generalized Born-GB electrostatic model). The electrostatic function chosen to be 'GB/VI' (Generalized Born/ volume integral) while the van der Waals function was depicted to be '800R3'. (800R3 simulates the repulsive part of vdw energies) the electrostatic interactions cutoff was kept at 15A. After protonation the protein crystal structures were energy minimized. For energy minimization the 'Amber10' force field while allowing adjustment to 'H-atoms'. The RMSD gradient was kept at '0.1 kcal/mol/A^2'.

### Ligand preparation

Two ligands were chosen for docking (1) Δ9-tetrahydrocannabinol (THC) (2) cannabidiol (CBD). The structures of THC and CBD were obtained from ZINC database with entry numbers: ZINC02039624 (THC)12 and ZINC04097407 (CBD)13 respectively. The ligands were optimized via energy minimization, using the 'Amber10' force field while allowing adjustment to 'H-atoms'. The RMSD gradient was kept at '0.1 kcal/mol/A^2'. (energy minimization is terminated when RMSD gradient falls below this value) This was carried out with the aid of Molecular Operating Environment (MOE) software (2019, demo version issued by the Chemical Computing Group), 14 as depicted in figure 3 and 4 respectively.

### Molecular docking

Prior to carrying out the docking protocol, determination of the essential amino acids in binding pockets was carried out with the help of literature. Docking for THC was conducting while keeping the known orthosteric site as the binding pocket; however, the CBD binding pocket was confirmed (via literature) in the N-terminal region of CB1, partially overlapping on the orthosteric site. A total of four docking jobs were carried out with the placement method chosen was 'Alpha Triangle' with post placement refinement kept as 'induced fit'. The initial scoring function was kept as 'London dG' and 'GBVI/WAS dG' as the final scoring function. No 'wall constraints' were used. The receptor was kept at 'Receptor' while receptor site was chosen to be 'Selected atoms'. The electronic density was depicted at 1σ with a resolution of 2.5. The search efficiency was kept at 100% (software provides 1-500% as an option). A total of 100 poses were generated for both active and inactive; out of which 45 (THC/activeCB1) and 68 (THC/inactiveCB1) poses were retained for THC, whereas for CBD 70 (CBD/activeCB1) and 100 (CBD/inactiveCB1) poses were retained by the software.

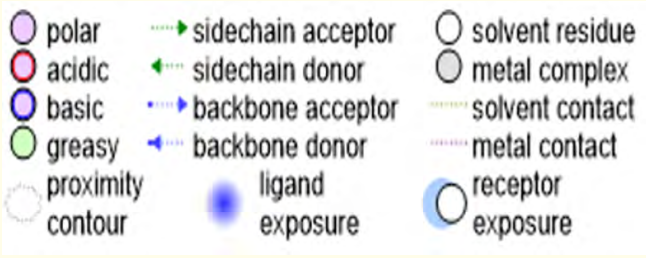


**Figure 5:** Ligand Intraction Key for MOE.

## Results and Discussion

A total of four docking jobs were carried out namely (1) THC-activeCB1 (2) THC- inactiveCB1 (3) CBD- activeCB1 (4) CBD- inactiveCB1, with the placement method chosen was 'Alpha Triangle' with post placement refinement kept as 'induced fit'. The initial scoring function was kept as 'London dG' and 'GBVI/WAS dG' was kept as the final scoring function, which yielded results closest to what's already reported in literature. 2D and 3D depiction of docking results of THC with active conformation of CB1 are shown in figure 6 and 7 respectively, while 2D and 3D depiction of docked THC with inactive conformation of CB1 are shown in figure 8 and 9.

Prior to docking, determination of the essential amino acids in binding pockets was carried out by comparing to the current literature. According to an article that conducted docking for Δ9-tetrahydrocannabinol (THC), Δ9-tetrahydrocannabivarin (THCV) and taranabant for the active and inactive conformation of CB1 receptor, the essential amino acids in orthosteric binding pocket that show interaction with the ligand Δ9-tetrahydrocannabinol (THC) are: PHE 268, LEU 193, VAL 196, PHE 379, PHE 170, PHE 174 and SER 383 for the active conformation, while for the inactive conformation PHE 268, LEU 193, PHE 102, PHE 379 and SER 383 residues were reported [15]. From figure 6 and 7 it is eminent that our docking results of THC, for the orthosteric binding pocket of the active conformation of CB1, were in agreement with the literature as the binding pocket can be seen with SER 383 interacting as a polar, side-chain donor with the OH group of the ligand, forming hydrogen bonds, whereas PHE 170 is seen forming aromatic interactions; residues LEU 193, VAL 196, PHE 379 and PHE 174 can also be seen in the pocket.

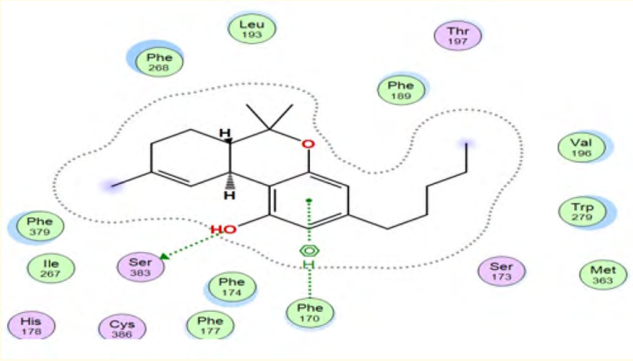


**Figure 6:** 2D ligand intractions of THC docked with Active CB1 receptor.

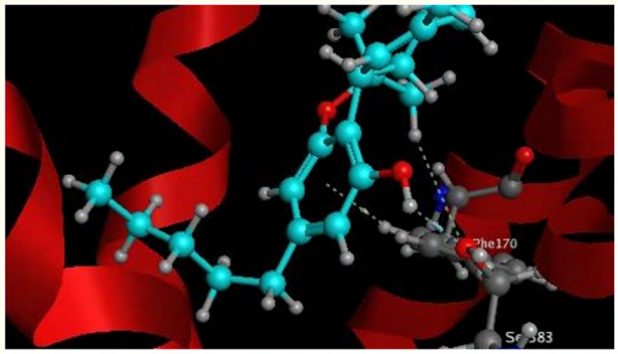


**Figure 7:** 3D ligand intractions of THC docked with Active CB1 receptor.

From figure 8 and 9 it can be seen that our results for THC docked in the orthosteric binding pocket of the inactive conformation of CB1 also mimic the results reported in the literature. In the binding pocket SER 383 can be seen as a polar backbone acceptor of the OH group of the ligand. We also found that, although SER 383 residue interacts with the ligand in both active and inactive conformation of the protein, the type of bond is different. PHE 268, PHE 102, PHE 379 residues can also be seen in the pocket.

Recreating these results validated our docking protocol for the purpose of finding binding pocket residues for CBD, as so far not enough research has been done on finding out the exact binding

pocket residues for the reported allosteric site to which CBD binds. According to literature the only suspected binding pocket for CBD was found near the N- terminal region of the CB1 receptor; it partially overlaps the orthosteric site and consists of CYS 107 [3].

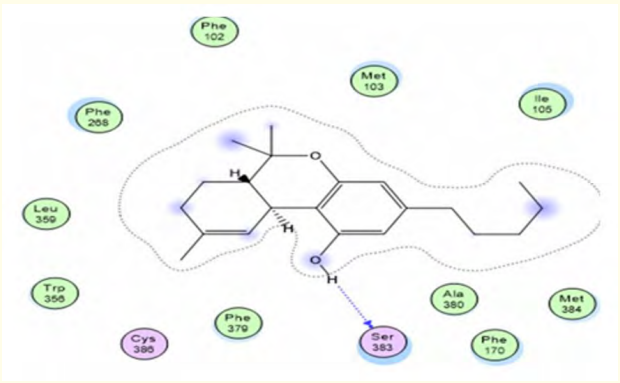


**Figure 8:** 2D ligand intractions of THC docked with Inactive CB1 receptor.

**Figure 9:** 3D ligand intractions of THC docked with Inactive CB1 receptor.

2D and 3D depiction of docking results of CBD with active conformation of CB1 are shown in figure 10 and 11 respectively; while 2D and 3D depiction of docked CBD with inactive conformation of CB1 are shown in figure 12 and 13.

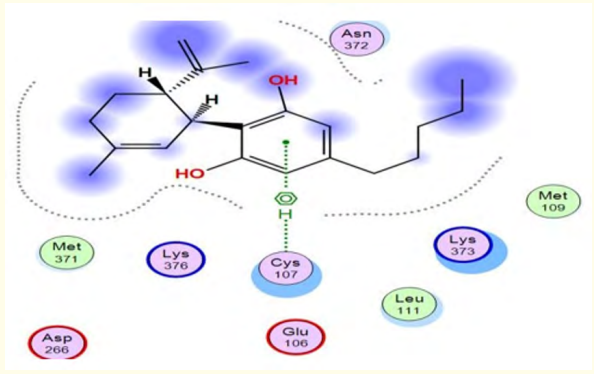


**Figure 10:** 2D ligand intractions of CBD docked with Active CB1 receptor.

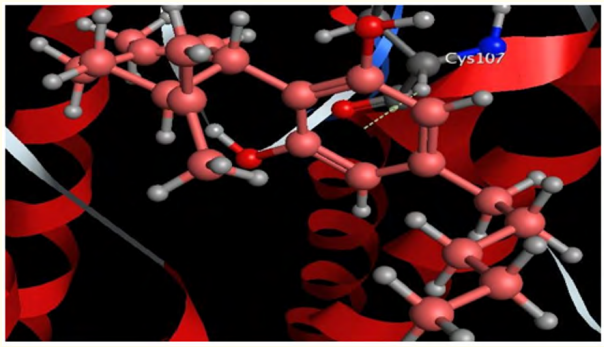


**Figure 11:** 3D ligand intractions of CBD docked with Active CB1 receptor.

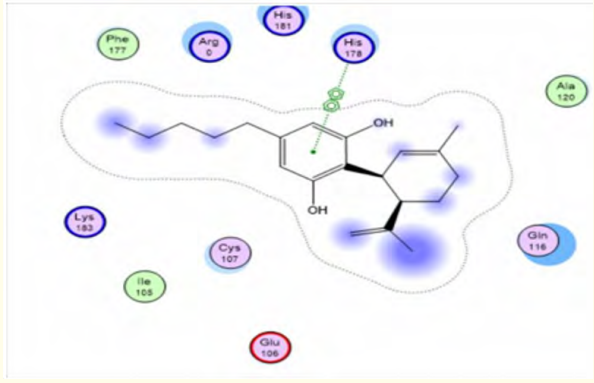


**Figure 12:** 2D ligand intractions of CBD docked with Inactive CB1 receptor.

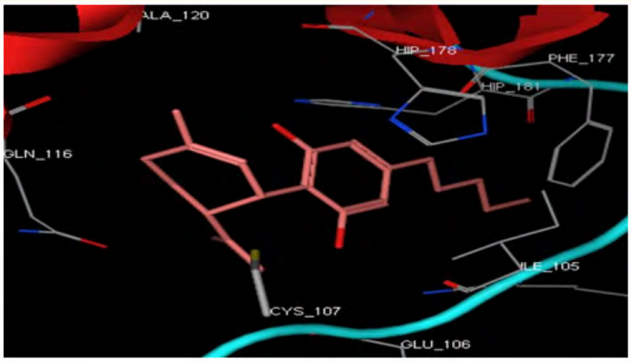


**Figure 13:** 3D ligand intractions of CBD docked with Inactive CB1 receptor.

In our results, docking done for CBD in the designated allosteric binding pocket in the active conformation of CB1 receptor protein, CYS 107 can be seen interacting in the form of aromatic interactions. Other residues that were found in the binding pocket were LYS 373, LEU 111, MET 109, ASN 372, LYS 376 and MET 371; 2D and 3D depictionof which can be seen in figure 10 and 11 respectively. In the inactive conformation of CB1 receptor the docking results of CBD interestingly showed no interaction with CYS 107, although it can be seen in the vicinity of the OH group of the ligand. Instead HIS 178 can be seen making aromatic interactions with the benzene group of the ligand. Apart from CYS 107 and HIS 178, residues we found common in the binding pocket for almost every ligand pose generated were GLN116, HIS 181, ARG 0, PHE 177 and ILE 105.

The correlation plot of the Generalized Born/ volume integral 'GB/VI' binding free energy and root mean square deviation 'RMSD' only for the active conformation of CB1 receptor with either of the ligands, THC and CBD depicted in figure 14 and 15 respectively. In either case the RMSD decreases with increase in the binding free energy. This is a clear indication that neither ligand is the true substrate of the receptor, nor can they be permanently bound to the receptor. Hence CBD can only provide temporary symptomatic relief when bound to the CB1 receptor. The ligands pose whose interactions are shown in figure 6, 7 and 10, 11 are highlighted in the correlation plots shown. The GB/VI binding energy is basically force-field-based free-energy estimate, with empirical terms to account for solvation and hydrophobic effect. Ideally the best pose is the one with the lowest binding free energy, which is not always the case but is the general trend. Although generally the lower the RMSD the better the binding pose but that is not always the case, often RMSD can't be the only descriptor one can rely on, other descriptors such as H-bond, van der Waal, electrostatic energy etc. are also taken under consideration (as shown in the tables below). Usually the inverse relation between RMSD and binding energy indicates that the ligand is unstable while bound to the receptor making it a reversible process. Hence making organically derived negative allosteric modulators (NAMS) such as CBD a good candidate for symptomatic relief in many neurodegenerative diseases.

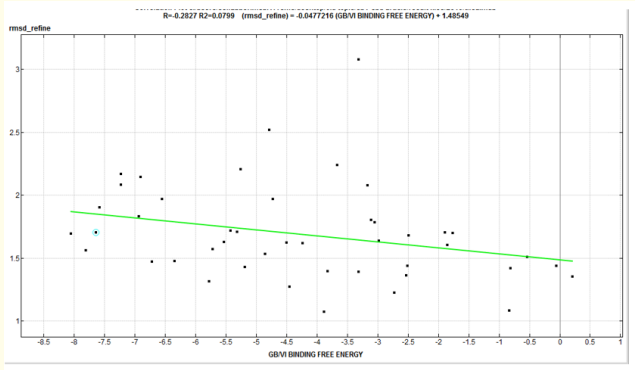


**Figure 14:** Correlation plot of GB/VI Binding Free Energy and RMSD for THC and active.

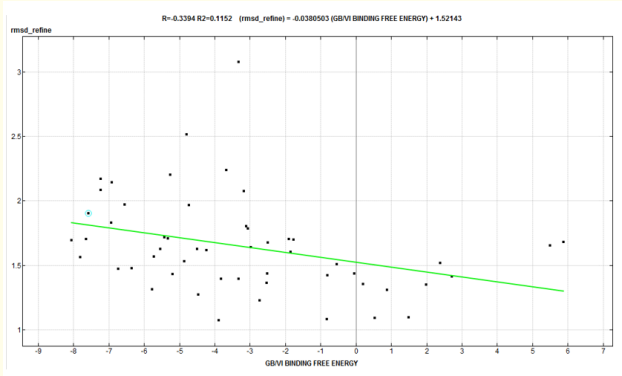


**Figure 15:** Correlation plot of GB/VI Binding Free Energy and RMSD for CBD and active.

The solution tables for docking scores of THC with the active and inactive conformation of CB1 receptor are presented in table 1 and 2 respectively; while solution tables of the docking scores of CBD in the active and inactive conformation of CB1 receptor are presented in table 3 and 4.

| Rank | Solution Number | Binding Free Energy (Kcal/mol) | Electrostatic Interaction Energy (Kcal/mol) | Van der Wall Interaction Energy (Kcal/mol) |
|---|---|---|---|---|
| 1 | 4 | -7.6 | -29.931079 | 14.577954 |
| 2 | 2 | -7.8 | -31.445491 | 18.405542 |
| 3 | 7 | -6.9 | -29.907411 | 15.888993 |
| 4 | 8 | -6.9 | -29.511219 | 15.656712 |
| 5 | 9 | -6.7 | -29.988674 | 19.663869 |
| 6 | 12 | -5.8 | -29.586723 | 24.527944 |
| 7 | 20 | -4.8 | -39.838970 | 25.110862 |
| 8 | 22 | -4.5 | -32.568565 | 28.524700 |
| 9 | 25 | -3.8 | -30.046739 | 25.577882 |
| 10 | 32 | -3.0 | -31.827705 | 27.018493 |

**Table 1:** The docking scores of THC in the active conformation of cb1.

| Rank | Solution Number | Binding Free Energy (Kcal/mol) | Electrostatic Interaction Energy (Kcal/mol) | Van der Wall Interaction Energy (Kcal/mol) |
|---|---|---|---|---|
| 1 | 2 | -8.9 | -7.8284912 | 873.85352 |
| 2 | 3 | -8.7 | 4.7227883 | 6795.4702 |
| 3 | 4 | -8.3 | 1.6609291 | 1311.996 |
| 4 | 5 | -8.2 | 0.53977686 | 399.54703 |
| 5 | 6 | -8.1 | -1.4235452 | 538.09772 |
| 6 | 7 | -8.0 | -0.88659167 | 1124.7869 |
| 7 | 8 | -7.9 | 23.672499 | 43619.512 |
| 8 | 9 | -7.9 | 7.2765393 | 1678.5289 |
| 9 | 11 | -7.7 | 6.9129095 | 22555.105 |
| 10 | 43 | -5.8 | 3.0987926 | 1879.2039 |

**Table 2:** The docking scores of THC in the Inactive conformation of cb1.

| Rank | Solution Number | Binding Free Energy (Kcal/mol) | Electrostatic Interaction Energy (Kcal/mol) | Van der Wall Interaction Energy (Kcal/mol) |
|---|---|---|---|---|
| 1 | 1 | -7.9 | 0.56999183 | 167.27705 |
| 2 | 2 | -7.8 | 3.0755842 | 107.48508 |
| 3 | 3 | -7.7 | 0.54624021 | 68.696846 |
| 4 | 4 | -7.5 | 53.958946 | 163279.33 |
| 5 | 5 | -7.4 | -18.720549 | 323811.13 |
| 6 | 6 | -7.2 | 29.038626 | 75036.039 |
| 7 | 7 | -7.2 | 3.7241356 | 11095.856 |
| 8 | 8 | -6.9 | -1.9372739 | 136.39922 |
| 9 | 9 | -6.5 | -2.8924136 | 1256.1271 |
| 10 | 20 | -6.1 | 12.9432 | 1427.1877 |

**Table 3:** The docking scores of CBD in the Active conformation of cb1

| Rank | Solution Number | Binding Free Energy (Kcal/mol) | Electrostatic Interaction Energy (Kcal/mol) | Van der Wall Interaction Energy (Kcal/mol) |
|---|---|---|---|---|
| 1 | 1 | -11.3 | 414.82849 | 5.66816 |
| 2 | 3 | -10.1 | 969.04236 | 3.6874416 |
| 3 | 2 | -10.1 | 226.9928 | -3.3954532 |
| 4 | 4 | -10.0 | 1315.8282 | 16.088272 |
| 5 | 5 | -9.9 | 33117.297 | -20.228025 |
| 6 | 6 | -9.8 | 1344.9482 | 13.12059 |
| 7 | 7 | -9.8 | 483.0206 | 3.1454813 |
| 8 | 8 | -9.7 | 1812.9214 | -36.065151 |
| 9 | 9 | -9.6 | 148.90756 | -5.4432611 |
| 10 | 11 | -9.5 | 81.599266 | 3.1844382 |

**Table 4:** The docking scores of CBD in the Inactive conformation of cb1.

Plant based cannibinods such as THC and CBD also offer neuro-protective properties; so far following evidence has been documented: (1) phenolic rings in cannabinoids protect against glutamate excitotoxicity which as exacerbate symptoms in neuro-degenerative disorders (2) The CB1 receptor has shown the ability to protect the nigrostriatal(NS) dopaminergic neurons against the

toxic effects of the neurotoxin hence protecting against microglia-mediated oxidative stress. (3) plant based cannabinoids such as CBD and THC show reduction the formation of the pro-inflammatory cytokines interleukin- 1β, interleukin-6 and interferon-β (4) some of the phyto-cannabinoid and the synthetic cannabinoid show neuro-protective action that does not seem to be entirely dependent on cannabinoid receptor activation, which brings us back to the fact that long term CB1 receptor activation can exacerbate motor function (5) stimulation of CB1 receptors by exogenous agonists can help control defects of transmission responsible for the generation of L-dopa induced dyskinesia, hence making plant based cannabinoids safer option than L-dopa based treatment. (6) the role of THC activation of cannabinoid system in reducing neuro-inflammation, most likely via the CB2 receptor, and creating an environment which supports neuronal survival by reducing excitotoxicity, promoting growth factor production and directly interfering with the cell death cascade [4,16,17].

## Conclusion

The negative values of the binding energy showed that the interactions were quite favorable in both active and inactive conformation, however both ligands show higher binding energy in the inactive conformation; which can be explained by the fact that it has been previously reported that ligand bind most rapidly to the inactive conformation, however detaches most slowly from the active conformation. Hence, each conformation provides an advantage to binding [18]. It was also observed that during the active conformation of CB1 Cannabinoid receptor, the cannabidiol (CBD) ligand binds to the allosteric site near the N-terminal, forming hydrogen bonds with the CYS 107; however, for the inactive conformation of CB1 Cannabinoid receptor, the cannabidiol (CBD) ligand forms aromatic inactions with HIS 178 instead of bonding with the CYS 107, hence making CYS 107 important for ligand-protein interaction during the active conformation.

The future of plant based cannabinoids in medicine especially in neurodegenerative disorders is nothing but bright and rightfully so, as they act on the same neurological pathways that neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PA), and Huntington's disease (HD) disrupt; cannabinoids could in theory be useful in treating these disorders; with recent legalization of medical marijuana the experimental work and research have all sky rocketed. Although persuasive basic evidence exists for the role of cannabinoids in movement, clinical evidence for their usefulness in relieving the symptoms of movement disorders is lacking simply due to lack of intensive investigation which is being made up for in the recent years. The future of marijuana and its active cannabinoids THC and CBD as medicine have four global recommendations (1) Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the better understanding of the natural cannabinoids found in the body should take place. (2) Clinical trials of cannabinoid drugs should be encouraged, especially in disorders in which symptom management is the major goal. (3) Studies to define any health related risks of smoking marijuana should be conducted. (4) Interaction between cannabinoids and cannabinoid signaling system and their effect on the dopaminergic neurons should be studied in depth [1,9,19-21].

## Acknowledgment

We are grateful for the supercomputing research and education center (ScREC) at Research Center for modeling and Simulation (RCMS) NUST, Pakistan for providing facility of supercomputer to carry out this research.

## Conflict of Interest

No conflict of interest.

## Bibliography

1. Lowenthal EA. "Marijuana as Medicine". 274 (1995).
2. Ai R and Chang CE. "A. Ligand-Specific Homology Modeling of Human Cannabinoid (CB1) Receptor". *Journal of Molecular Graphics and Modelling* 38 (2012): 155-164.
3. Sabatucci A., *et al*. "In Silico Mapping of Allosteric Ligand Binding Sites in Type-1 Cannabinoid Receptor". *Biotechnology and Applied Biochemistry* 65.1 (2018): 21-28.
4. BROTCHIE J. CB "Cannabinoid Receptor Signalling in Parkinson's Disease". *Current Opinion in Pharmacology* 3 (2003): 54-61.
5. Welsh WJ., *et al*. "Homology Model of the CB 1 Cannabinoid Receptor: Sites Critical for Nonclassical Cannabinoid Agonist". 71 (2003): 169-189.
6. Tanveer R., *et al*. "Cannabinoid Receptors and Neurodegenerative Diseases". *Wiley Interdisciplinary Reviews: Membrane Transport and Signaling* 1 (2012): 633-639.

7. Reggio PH. "Endocannabinoid Binding to the Cannabinoid Receptors: What Is Known and What Remains Unknown". *Current Medicinal Chemistry* 17.10 (2010): 1468-1486.

8. Durdagi S., *et al*. "Computational Study on Cannabinoid Receptors and Potent Bioactive Cannabinoid Ligands: Homology Modeling, Docking, de Novo Drug Design and Molecular Dynamics Analysis". *Molecular Diversity* 14.2 (2010): 257-276.

9. Fife TD., *et al*. "Clinical Perspectives on Medical Marijuana (Cannabis) for Neurologic Disorders". *Neurology Clinical Practice* 5 (2015): 344-351.

10. Hua T., *et al*. "Crystal Structure of the Human Cannabinoid Receptor CB1". *Cell* 167 (2016): 750-762.e14.

11. Hua T., *et al*. "Crystal Structures of Agonist-Bound Human Cannabinoid Receptor CB1". *Nature* 547 (2017): 468-471.

12. ZINC02039624. ZINC Is Not Commercial - A database of commercially-available compounds.

13. ZINC04097407. ZINC Is Not Commercial - A database of commercially-available compounds.

14. Chemical Computing Group (CCG). Computer-Aided Molecular Design.

15. Jung SW., *et al*. "Exploring the Ligand Efficacy of Cannabinoid Receptor 1 (CB1) Using Molecular Dynamics Simulations". *Science Report* 8.1 (2018): 13787.

16. More SV., *et al*. "Promising Cannabinoid-Based Therapies for Parkinson's Disease: Motor Symptoms to Neuroprotection". *Molecular Neurodegeneration* 10 (2015): 17.

17. Dí ez-Cirarda., *et al*. "Neurorehabilitation in Parkinson's Disease: A Critical Review of Cognitive Rehabilitation Effects on Cognition and Brain". *Neural Plasticity* (2018): 1-12.

18. Yakovenko O., *et al*. "Inactive Conformation Enhances Binding Function in Physiological Conditions". *Proceedings of the National Academy of Sciences of the United States of America* 112.32 (2015): 9884-9889.

19. Kindred JH., *et al*. "Cannabis Use in People with Parkinson's Disease and Multiple Sclerosis: A Web-Based Investigation. Complement". *Therapy Medicine* 33 (2017): 99-104.

20. Benbadis SR., *et al*. "Medical Marijuana in Neurology". *Expert Review of Neurotherapeutics* 14 (2014): 1453-1465.

21. Barnes DPsychol JC. Cannabis: The Evidence for Medical Use Professor Michael P Barnes MD FRCP Honorary Professor of Neurological Rehabilitation, Newcastle University (2016).

**Volume 3 Issue 9 September 2019**