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Research Article

Cannabis Compounds: Docking and Dynamics Study

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Abstract

Cannabis molecules exhibit significant therapeutic potential, offering promising prospects in healthcare. This in silico study aims to evaluate the affinity and stability of non-psychotropic cannabis-derived compounds (CBC, CBD, CBG, CBN, and β-Cannabispiranol) with CB1 and CB2 receptors to identify the ligand with the highest interaction potential.

Using MOE (Molecular Operating Environment) for molecular docking and GROMACS for molecular dynamics simulations, the interactions between these ligands and their targets were analyzed. Results reveal that cannabis compounds interact favorably with both CB1 and CB2 receptors, with a clear preference for CB2.

CBG demonstrated the highest affinity with CB2 (-7.9008 kcal/mol), forming two key bonds: an H-arene bond and a hydrogen bond with phenylalanine 183. The CB2-CBG complex exhibited remarkable stability over 8000 ps, with an RMSD of 0.6993 Å. CBD showed the best affinity with CB1 (-7.4857 kcal/mol), forming a hydrogen bond with methionine 363 and an RMSD of 1.6918 Å, also within acceptable limits.

In conclusion, CBG emerges as the most promising ligand due to its stable, reversible interaction and high affinity potential with CB2.

Keywords: Cannabinoids, molecular docking, molecular dynamics, type 1 cannabinoid receptors, type 2 cannabinoid receptors.

INTRODUCTION:

Cannabis sativa is an annual, dioecious flowering plant with characteristic palmate leaves and a distinctive venation pattern. There are three known subspecies of *Cannabis*: *Sativa*, *Indica*, and *Ruderalis*. *Cannabis sativa* is the most widespread variety, growing in both tropical and temperate climates[1]. *Cannabis sativa* contains 545 chemical compounds, of which 104 are cannabinoids, while the others include flavonoids, terpenes, fatty acids, etc[2]. The best-characterized cannabinoid constituent is D9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis[2], and the plant's psychotropic effects are attributed to its content of this class of compounds[3]. Other important non-psychoactive components with several medical functions[3] include cannabidiol (CBD), cannabinol (CBN)[2] cannabichromène (CBC) cannabigerol (CBG)[4], and cannabispirol or β-Cannabispiranol[4].

The development of cannabinoids as therapeutic agents and their use in medical applications have been studied due to their antinociceptive, anti-inflammatory, antioxidant, antimicrobial, and anti-biofilm effects[5] Anxiolytic, antidepressant, and antipsychotic[6]. Such properties have the potential to be used in the therapeutic approach of a number of devastating diseases, for example, glaucoma, depression, neuralgia, multiple sclerosis, Alzheimer's disease, as well as the managing of HIV and cancer related symptoms[3]. They are also being studied for the treatment of acne[7], Skin cancer, psoriasis, dermatitis, and scleroderma[8], Inflammatory bowel diseases[5], Cardiovascular diseases, epilepsy[8], For appetite stimulation and obesity risk reduction[9].

Cannabinoids exert their effects by activating two distinct G protein-coupled receptors, called type 1 (CB1) and type 2 (CB2) cannabinoid receptors[10]. The CB1 receptor is strongly expressed in the central nervous system (CNS) and along pain pathways [10, 2]. In contrast, the CB2 receptor is primarily, but not exclusively, located outside the CNS, with dense expression in peripheral tissues involved in immune functions [10, 2].

Molecular docking is a computational study to estimate the most likely configuration and orientation of a molecule, called ligand, that binds it into its target on the basis of their structures[11]. Its purpose is the modeling the critical interaction between the two molecules, whose three-dimensional structures are already known,

in order to estimate the binding affinity[12]. Molecular docking has been an important tool to realize drug development faster, cheaper and more efficient[11]. The principle of molecular docking is based on the aforementioned "lock and key" model. Here, the lock is defined as a macromolecular receptor having various architectures, and the key is a small ligand with a defined architecture. If the macromolecular receptor and ligand are compatible enough, with appropriate geometry, it results in electrostatic, hydrogen bonds and hydrophobic interactions. During the docking process, the conformations of the ligand and the nearby amino acid residues are gradually changed, fitting themselves to each other, to generate a proper binding[13].

The main component of cannabis, THC, strongly activates the CB1 cannabinoid receptor and also modulates the CB2 cannabinoid receptor, but this molecule has psychoactive effects[14]. The formation of a covalent bond between the ligand and the target is essential for a number of effective drugs[15]. The objective of this study is to perform molecular docking of non-psychomimetic cannabis-derived compounds, namely CBC, CBD, CBG, CBN, and β-Cannabispiranol, with CB2 and CB1 receptors. This study aims to identify the ligand with the highest interaction potential with the appropriate cannabinoid receptors, as well as to analyze the type of interaction, the nature of the bond, and the stability of this interaction.

METHODOLOGY :

1. Molecular docking using Molecular Operating Environment (MOE).

MOE (*Molecular Operating Environment*) is a software platform for drug design that combines visualization, modeling, and simulations. This approach is an extremely fast tool, useful for large-scale virtual screening, differentiating molecules that can or cannot interact, and ranking active compounds among them based on their binding affinities[16].

To investigate the molecular docking of *cannabis sativa* compounds ; CBC, CBD, CBG, CBN, and β-Cannabispiranol—with human CB1 and CB2 receptors, we used the prediction method with MOE 2022.02 software. The crystallographic structures of the active conformations of CB1 and CB2 were downloaded from the Protein Data Bank (PDB) at (https://www.rcsb.org/) in PDB format. The chemical structures of CBC, CBD, CBG, and CBN were extracted from the Drug Data Bank chemoinformatics library (https://go.drugbank.com/), while β-Cannabispiranol was obtained from the MedChemExpress chemoinformatics library (https://www.medchemexpress.com). Once the active compounds and targets were prepared, molecular docking was initiated by setting 30 poses for the interaction between the ligands and targets, followed by the selection of the five best conformations with the ligands.

2. Molecular dynamics (MD)

In this study, we conducted two separate molecular dynamics simulation experiments, focusing primarily on RMSD (*Root Mean Square Deviation*) trajectory analysis. The *CHARMM-modified* water model *TIP3P* was used as the solvent in the simulations, and the protein ends were terminated with “NH3+” and “COO-” groups. The *CHARMM36* force field was chosen to model the protein topology in both experiments. The topologies of the ligands, WI5 agonist and cannabigerol, were generated using the SwissParam tool on the SwissADME server. In the first experiment, we simulated the 6PT0 protein in complex with its WI5 agonist. In the second experiment, we formed a complex between the 6PT0 protein and cannabigerol. 6PT0 is a membrane protein of homos sapiens, composed of five chains or molecules (R, A, B, C, E), and interacts with three ligands: WI5, cholesterol and palmitic acid. The ligand of interest is WI5 (formula: C27H26N2O3, WIN 55,212-2), since it interacts with the R chain representing the CB2 receptor[17]. WIN 55,212-2 is a chemical compound known to produce effects similar to those of cannabinoids, such as tetrahydrocannabinol (THC). It is a potent cannabinoid receptor agonist, and has demonstrated notable efficacy as an analgesic in rat models of neuropathic pain[18], so it was chosen as the reference ligand. The RMSD trajectory was our main metric for quantifying structural fluctuations and deviations of the protein and ligands throughout the simulations. All simulations were carried out using GROMACS software, pre-equilibrating the systems under constant temperature and pressure conditions (NVT and NPT). Each simulation was extended over 10 nanoseconds, to capture significant structural changes between the 6PT0 protein and its ligands.

RESULTS

1. Studies on molecular docking between cannabis molecules CBC, CBD, CBG, CBN, β-Cannabispiranol with CB2 and CB1 receptors.

We started by examining the S-scores (in kcal/mol) and RMSD values of the interactions, as well as identifying the best pose for each ligand. These data are presented in Tables **1** and **2**.

The S-score refers to the affinity between the ligand and the protein, quantitatively measuring the quality or relevance of a given molecular conformation or interaction, based on predefined specific criteria. The choice of the conformation in which the ligand has the best interaction with the protein depends on the structure with the lowest energy[16].

RMSD (*Root Mean Square Deviation*): The RMSD of the heavy atoms between a predicted pose and the observed pose in the unmodified crystal structure was used as a measure for the accuracy of the prediction, by aligning the two datasets to be compared, for example, two molecular structures, and measuring the distance between each pair of corresponding elements in the two datasets. A smaller RMSD means that the two datasets are more similar or closer to each other in their spatial arrangement.

Table 1: RMSD and SCORE results of cannabis molecules studied with CB1 and CB2 receptors.

Compounds bound to CB2	S- score (kcal/mol)	RMSD (Å)	Compounds bound to CB1	S- score (kcal/mol)	RMSD (Å)
CBC	-7.6834	1.5461	**CBC**	-7.3101	4.5194
CBC	-7.6548	1.4800	**CBC**	-7.1838	2.0638
CBC	-7.5521	1.3528	**CBC**	-7.1290	1.6668
CBC	-7.3943	2.8420	**CBC**	-7.0477	2.5547
CBC	-7.3274	1.5820	**CBC**	-7.0416	1.7632
CBD	-7.6316	1.0795	**CBD**	-7.4857	1.6918
CBD	-7.4353	1.2913	**CBD**	-7.1923	1.4054
CBD	-7.3894	2.1734	**CBD**	-7.1497	1.6111
CBD	-7.2864	1.1970	**CBD**	-6.9697	1.6240
CBD	-7.2566	1.2395	**CBD**	-6.9621	1.4475
CBG	-7.9008	0.6993	**CBG**	-7.3121	2.6232
CBG	-7.7416	1.7020	**CBG**	-7.2497	0.8958
CBG	-7.7019	2.5419	**CBG**	-7.2153	1.1299
CBG	-7.6146	1.4176	**CBG**	-7.1695	1.1595
CBG	-7.5950	2.4207	**CBG**	-7.1657	1.3015
CBN	-7.3548	1.0219	**CBN**	-7.2195	0.9244
CBN	-7.2431	1.5247	**CBN**	-7.1483	2.3861
CBN	-7.0169	1.0699	**CBN**	-6.8134	2.8798
CBN	-7.0122	1.3036	**CBN**	-6.7647	2.3540
CBN	-6.9448	2.0753	**CBN**	-6.6538	1.5567
β-Cannabispiranol	-6.2986	0.6790	**β-Cannabispiranol**	-6.5163	0.9972
β-Cannabispiranol	-6.2659	1.3951	**β-Cannabispiranol**	-6.3373	1.6292
β-Cannabispiranol	-6.2565	0.5478	**β-Cannabispiranol**	-6.0619	1.3440
β-Cannabispiranol	-6.2418	1.5612	**β-Cannabispiranol**	-6.0342	1.1029
β-Cannabispiranol	-6.2107	1.3157	**β-Cannabispiranol**	-6.0320	0.9568

Table 2: Results of the Best RMSD and SCORE for CB1 and CB2 Receptors with the Studied Ligands.

Compounds bound with CB2	S- score (kcal/mol)	RMSD (Å)	Compounds bound with CB1	S- score (kcal/mol)	RMSD (Å)
WI5	-9.0346	2.2461	KCA	-8.0485	1.7749
CBC	-7.6834	1.5461	CBC	-7.3101	4.5194
CBD	-7.6316	1.0795	**CBD**	**-7.4857**	**1.6918**
CBG	**-7.9008**	**0.6993**	CBG	-7.3121	2.6232
CBN	-7.3548	1.0219	CBN	-7.2195	0.9244
β-Cannabispiranol	-6.2986	0.6790	β-Cannabispiranol	-6.5163	0.9972

1. 1 Study of the molecular docking interactions.

1.2 Study of the molecular docking interactions between the cannabinoid receptor type 2 and the reference ligand WI5.

This figure highlights the molecular interactions between the reference ligand WI5 and the key residues of the active site of the cannabinoid receptor type 2 (CB2).

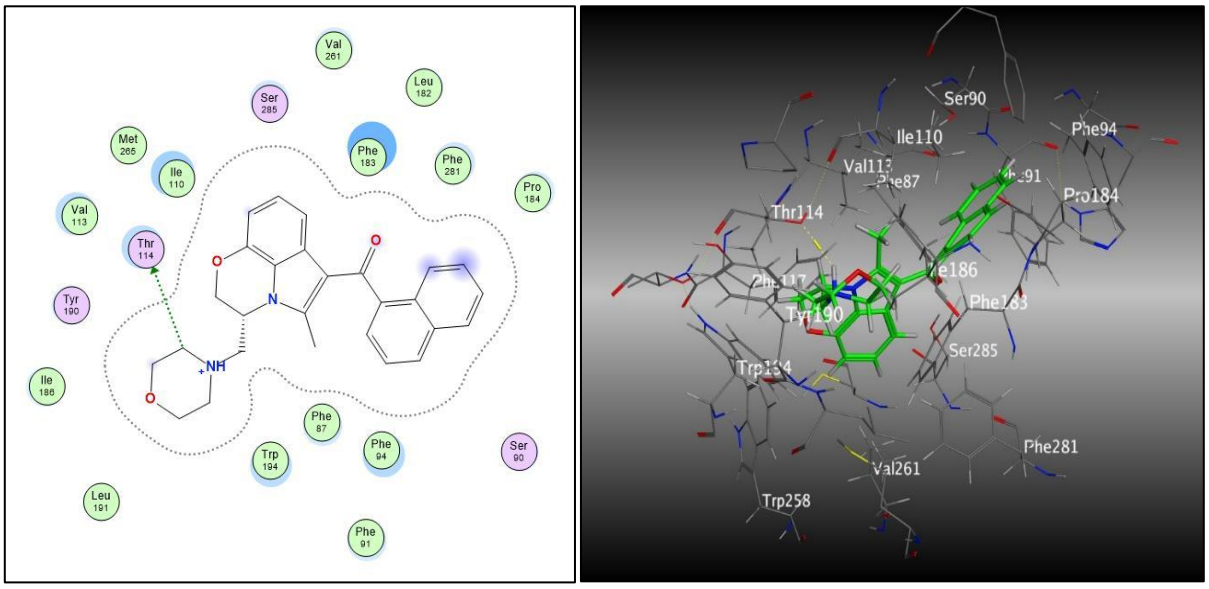

Figure 1: Interactions of the reference ligand WI5 in the active site of the CB2 receptor.

1.3 The study of molecular docking interactions between the type 2 cannabinoid receptor and the cannabigerol ligand.

This figure highlights the molecular interactions between the CBG ligand and key residues of the active site of the type 2 cannabinoid receptor (CB2).

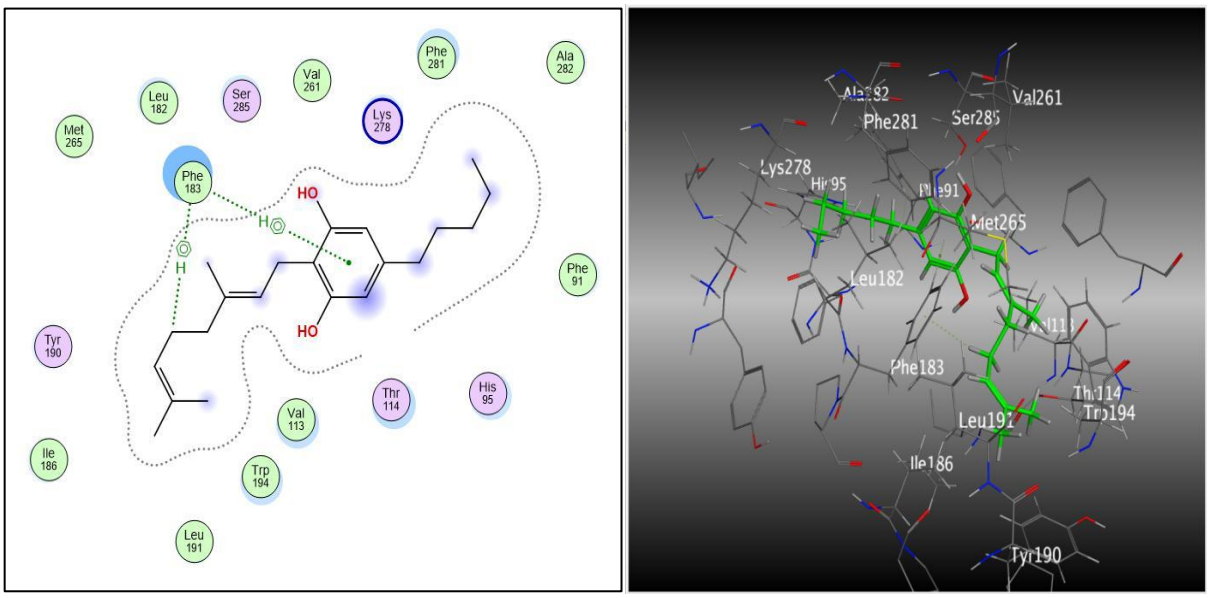

Figure 2: The interactions of the CBG ligand in the active site of the CB2 receptor.

1.4 The study of molecular docking interactions between the cannabinoid receptor type 1 and the reference ligand KCA.

This figure highlights the molecular interactions between the reference ligand KCA and the key residues of the active site of the cannabinoid type 1 receptor (CB1).

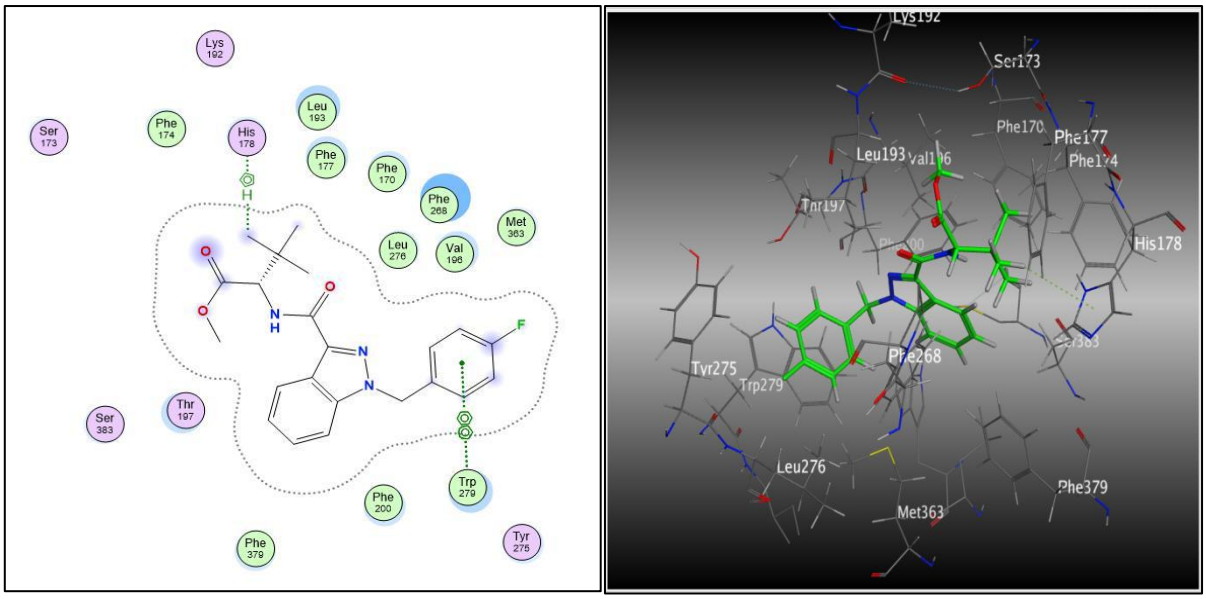

Figure 3: The interactions of ligand KCA in the active site of the CB1 receptor.

1.5 Study of Molecular Docking Interactions Between the Type 1 Cannabinoid Receptor and the Ligand Cannabidiol:

This figure highlights the molecular interactions between the ligand CBD and key residues within the active site of the type 1 cannabinoid receptor (CB1).

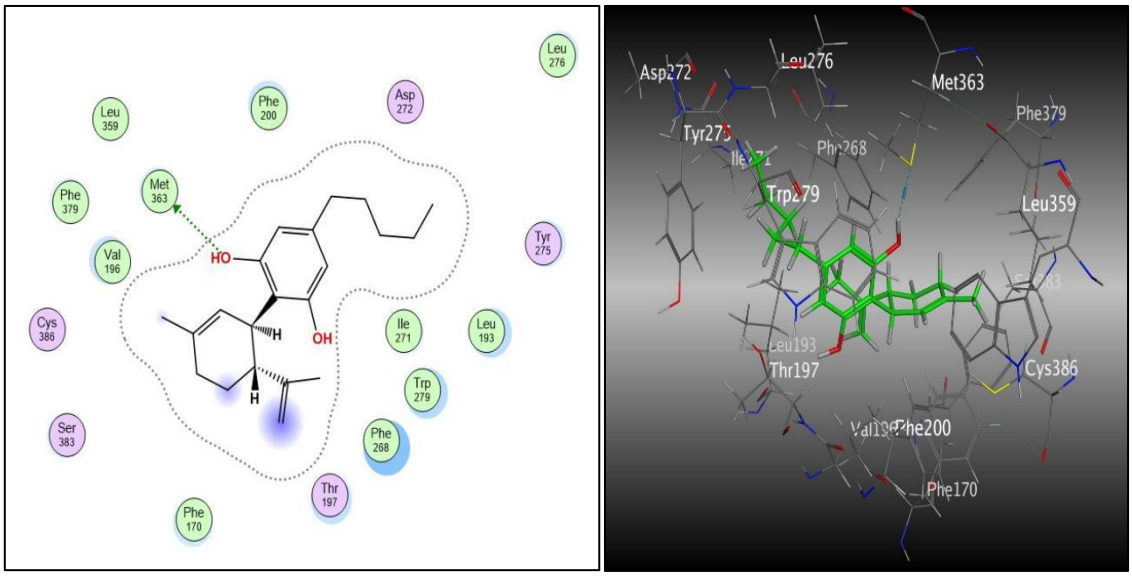

Figure 4: The interactions of ligand CBD in the active site of the CB1 receptor.

2. Molecular dynamics

Molecular dynamics (MD) simulation is an essential technique for studies involving *in silico* drug discovery[19], including the longest simulations ever carried out, has been widely used for prediction. DM simulations are a mature technique that can be used effectively to understand macromolecular structure-function relationships. One of the most practical applications of the molecular recognition concept concerns docking strategies, whether for small molecules or proteins. Understanding how a ligand, usually a substrate or regulator, binds to its macromolecular counterpart is a key issue in understanding function itself, and forms the basis of structural drug design. The recognition process is by nature dynamic[20].

The root-mean-square deviation (RMSD) of the whole system and of each residue respectively were calculated from the trajectories generated from the production stage[19].

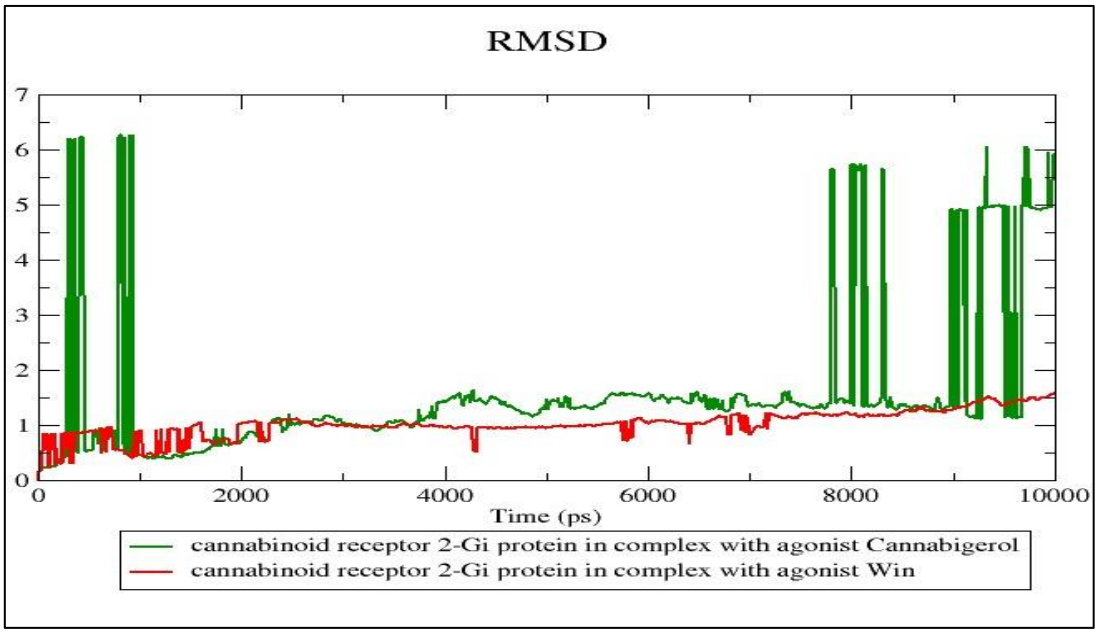

Figure 5 : RMSD analysis for MD simulations for CB2 and CBG (green) and the co-crystallized reference CB2 and WI5 (red).

DISCUSSION:

The results of molecular docking performed using the MOE software provide valuable insights into the affinity of ligands for targets and key molecular-level interactions. According to Table 1, Cannabis sativa molecules CBC, CBD, CBG, and CBN show a preference for interacting with the CB2 receptor over CB1, as suggested by the more negative scores obtained when interacting with CB2 (CBC = -7.6834 Kcal/mol, CBD = -7.6316 Kcal/mol, CBG = -7.9008 Kcal/mol, CBN = -7.3548 Kcal/mol, β-Cannabispiranol = -6.2986 Kcal/mol) compared to CB1 (CBC = -7.3101 Kcal/mol, CBD = -7.4857 Kcal/mol, CBG = -7.3121 Kcal/mol, CBN = -7.2195 Kcal/mol, β-Cannabispiranol = -6.5163 Kcal/mol). Additionally, the RMSD is lower in the interaction with CB2. In contrast, β-Cannabispiranol shows a preference for interacting with CB1 over CB2 (see Table 1).

The molecule with strongest affinity to CB2 receptor is CBG. It gave the best docking energy score, to "-7.9008 kcal/mol" (Table 2). A more negative score indicates a more stable molecular binding[21]. Moreover, CBG has an RMSD value less than 2, low distance between CBG and the reference ligand WI5. By comparing the affinity score to CBG (-7.9008 kcal/mol) and the corresponding co-crystallized ligand WI5 (-9.0346 kcal/mol) we find that CBG has a slightly lower affinity than WI5, although the difference is still in an acceptable scenario. CBG produced an interaction between CB2 with an affinity of -7.9008 kcal/mol and a distance of 0.6993 Â. Luciano De Petrocellis et al. Tested 11 cannabis derivatives against TRPV1, TRPV2, TRPM8 and TRPA1 targets and identified CBG and THC as the most potent antagonists towards TRPM8 (Transient Receptor Potential Melastatin 8), thereby affecting pain modulations[22]. Therefore, the CBG molecule is effective not only to the CB2 receptor, but also to other targets.

The molecule with the highest binding affinity to CB1 receptor is CBD (Table 2). Achieving the highest docking energy score (-7.4857 kcal/mol) representing the most stable docking with the CB1 receptor. Furthermore, CBD shows an RMSD value <2, specifically 1.6918 Å (Table 2), indicating high binding affinity towards CB1. Comparing the affinity score obtained for CBD (-7.4857 kcal/mol) with that of the co-crystallized ligand (reference ligand) KCA (-7.5140 kcal/mol) (Table 2), we observe that CBD has an affinity equal to that of KCA. CBD produced an interaction on CB2 with a binding energy of -7.4857 kcal/mol and a distance of 1.6918 Å.

The RMSD of the co-crystallized reference ligand WI5, determined by the MOE software, reflects the conformation of the position on the reference ligand molecule at the interaction site with the CB2 receptor, and it is 2.2461 Å (Table 2). The tested ligand CBG (highest affinity for CB2), with the lowest RMSD value (Table 1), is considered. It is interesting to compare the RMSD of the atoms of the tested ligand and reference ligand CBG, with respect to the conformation of the reference ligand WI5. The value of 0.6993 Å indicates the average deviation of the atomic positions of the CBG ligand compared to the conformation of the reference ligand WI5 when bound to the CB2 receptor. An RMSD below 2 and close to 0 suggests that the tested ligand CBG has a better alignment or better fit with the reference conformation, which could indicate a stronger affinity for the CB2 receptor[23].

The RMSD of the reference ligand KCA with the CB1 receptor, according to the MOE software, has a value of 1.7749 Å (Table 2). When we examine the tested ligand CBD, which shows the highest affinity for CB1, its RMSD is 1.6918 Å (Table 2). This RMSD value below 2 suggests that CBD has a better alignment or a better fit with the conformation of the co-crystallized reference ligand[23], This could indicate a good affinity for the CB1 receptor. Luciano De Petrocellis et al. tested 11 cannabis derivatives on TRPV1, TRPV2, TRPM8, and TRPA1 (Transient Receptor Potential Ankyrin 1) targets, and they found that CBC, CBD, and CBN were powerful

desensitizers of rat TRPA1, which reduces the sensation of pain[22], Which highlights that CBG exerts significant effects on several key therapeutic targets.

The activation of CB1 and CB2 receptors by Cannabis sativa and its derivatives, cannabinoids, has shown beneficial effects in several medical fields. These receptors, integrated into the endocannabinoid system, are targeted to treat various conditions [24], [25].

To find among the screened cannabis molecules, the one with the highest potential for interaction with the cannabinoid receptors CB1 and CB2, it seemed prudent to study the interaction mechanisms first established by the reference ligand WI5 (C27H26N2O3), whose score is -9.0346 kcal/mol and RMSD is 2.2461 Å. The visualization of this compound's interactions within the active site of CB2 was carried out using the MOE software. It is observed that WI5 forms a bond with CB2 (Figure 1), and a hydrogen bond interaction is established between the NH2 group of the WI5 ligand and the Threonine 114 residue of CB2. The amino acid residues Val 261, Ser 285, Leu 182, Phe 183, Phe 281, Pro 184, Met 265, Ile 101, Val 113, Thr 114, Tyr 190, Ile 186, Leu 191, Trp 194, The 87, Phe 94, Phe 91, and Ser 90 participate in Van der Waals interactions with the CB2 compound (Figure 1).

The interaction of the CBG molecule with the active site of CB2 gives a score of -7.9008 kcal/mol and an RMSD of 0.6993 Å. However, this ligand forms two bonds (Figure 2). The first is an H-arene interaction formed between the benzene ring of the CBG ligand and the phenylalanine 183 amino acid residue of the CB2 receptor, and the second interaction is a hydrogen bond between the carbon of the CBG ligand and the phenylalanine 183 residue of the CB2 receptor (Figure 2). The amino acid residues Met 265, Leu 182, Ser 285, Val 261, Lys 278, Phe 281, Ala 282, Phe 91, His 95, Thr 114, Val 113, Trp 194, Leu 191, Ile 186, and Tyr 190 participate in Van der Waals interactions with the CB2 compound.

The interaction of the reference molecule KCA (chemical formula: C22H24FN3O3) with the active site of CB1. This compound shows a binding energy score of -8.0485 kcal/mol and an RMSD of 1.7749 Å. Using the MOE software, we visualized the interactions of this compound within the active site of CB1. It is observed that KCA forms two bonds with CB1 (Figure 3). The first is an arene-H interaction between Histidine 178 of CB1 and the carbon of the KCA ligand, and the second is an arene-arene interaction between the Tryptophan 279 residue of CB1 and the benzene ring of KCA. The amino acid residues Lys 192, Ser 173, Phe 174, Leu 193, Phe 177, Phe 170, Phe 268, Leu 276, Val 196, Met 363, Tyr 275, Phe 200, Phe 379, Thr 197, and Ser 383 participate in Van der Waals interactions with the CB2 compound (Figure 3).

The interaction of the CBD ligand with the active site of CB1 gives a score of -7.4857 kcal/mol and an RMSD value of 1.6918 Å. However, this ligand forms a hydrogen-donor bond between the hydroxyl (OH) group of the CBD ligand and the methionine 363 residue of the CB2 receptor (Figure 4). The residues Leu 276, Asp 272, Phe 200, Leu 359, Phe 379, Val 196, Cys 386, Ser 383, Phe 170, Thr 197, Phe 268, Trp 279, Ile 271, Leu 193, and Tyr 275 participate in Van der Waals interactions with the CB2 compound (Figure 4). The article by De Petrocellis et al. (2011) studies the effects of cannabinoids, including cannabidiol (CBD) and other cannabis extracts, on TRP (transient receptor potential) channels and endocannabinoid metabolic enzymes. Regarding the FAAH (Fatty Acid Amide Hydrolase) enzyme, responsible for the degradation of anandamide (an endocannabinoid), CBD was found to be a potent inhibitor. This means that CBD reduces FAAH activity, leading to an increase in anandamide levels, which can have anti-inflammatory and analgesic effects[22], Which reports that CBD has potent effects on several therapeutic targets.

The CBG molecule showed the best affinity score with the CB2 receptor, with a value of -7.9008 kcal/mol. These results justify the continuation of the study by focusing on the most promising ligand, CBG, and its potential target, the CB2 receptor. To analyze in more detail the proposed binding mode of CBG, various GROMACS scripts were used to calculate the hydrogen bond distances formed between CBG and the CB2 receptor and CB2-WI5.

Two MD simulation experiments were carried out on CB2-WI5 and CB2-CBG (Figure 5). At the start of the molecular dynamics simulation of the CB2-CBG and CB2-WI5 complexes (ref) from 0 to 1000 (Ps), the RMSD characterized by fluctuations, may be the result of the equilibration process, to reach a thermodynamic equilibrium state, so may be due to initial adjustments of atoms to reach stable configurations, so the simulation requires more time to reach a stable state.

From 1000ps to 2000ps, the RMSD of the stimulated CB2-CBG complex is lower and stable than that of the CB2-WI5 ref complex, which continues to fluctuate to reach maximum fluctuation (Figure 5). This means that the simulated complex has reached its thermodynamic equilibrium state and is in a stable conformation, while the ref complex has not yet found its stable conformation with its ligand.

From 2000ps to 8000ps, the RMSD of the stimulated CB2-CBG complex and the reference CB2-WI5 complex is stable; a low RMSD indicates high structural stability [23], [26], indicating that the conformation of the system during stimulation is close to the reference structure. This means that the system is well balanced and does not undergo drastic changes in structure, a prolonged period of stability suggests that the system is well balanced and retains a stable structure for a prolonged period, this may indicate that the simulation conditions are appropriate, the system is in a state of dynamic equilibrium, so it can be said that in this period both complexes retain a relatively constant molecular structure, balanced throughout this period, as well as there are no major changes in structure. This reinforces confidence in the simulation results. A stable RMSD over a long period may indicate that the simulated system has reached a state of thermodynamic equilibrium, indicating that the interactions between the atoms in the system are balanced and that the molecular structure retains

relative stability throughout the simulation[26]. The CB2 protein and CBG ligand in this period interact coherently and their conformation is maintained within an acceptable range compared with the reference structure.

From 8,000Ps to 10,000Ps the detection of fluctuations in the CB2-CBG reference complex could indicate that the binding becomes less stable, the CBG ligand progressively detaches from CB2, suggesting a reversibility of CB2-CBG binding, so CBG interacts with the CB2 target, exerts its pharmacological effect, once this effect is achieved, it dissociates from the target to be eliminated from the body. On the other hand, the RMSD of the CB2-WI5 reference complex is more or less stable, with a very gradual increase, so the ligand is still bound to the receptor. WI5, the synthetic form of cannabinoid, seems to have a covalent bond with the CB2 target, meaning that the bond is stronger and harder to break. The bond between CB2-WI5 is a time-limited reversible bond, the speed and time of ligand-target dissociation used by the reference complex being longer than that of the test complex, so the binding kinetics of the reference CB2-WI5 complex are slower than those of the test CB2-CBG complex, so it can be said that synthetic cannabis WI5 seems to have more side effects than natural cannabis CBG.

CONCLUSION:

The study was undertaken for molecular docking of non-psychomimetic cannabinoid compounds - CBC, CBD, CBG, CBN, and β-Cannabispiranol-with the CB2 and the CB1 receptors to find out which ligand can interact most strongly and study the type, nature, and stability of these interactions.

They concluded from these results that...

CBG has a strong affinity for the CB2 receptor, with a docking score of -7.9008 kcal/mol and a very low RMSD value of 0.6993 Å, showing the formation of stable interaction with the receptor, well aligned with that of the reference ligand WI5.

CBD shows the highest binding affinity towards CB1 receptor with a docking score of -7.4857 kcal/mol and an RMSD value of 1.6918 Å, validating the formation of a stable interaction comparable with reference ligand KCA.

Other compounds (i.e., CBC, CBN, β-Cannabispiranol) show moderate affinities and less stable binding profiles with each profile showing its own preference between CB1 or CB2.

Molecular dynamics simulations performed through GROMACS support the view of the stability of CB2-CBG and CB1-CBD complexes over relatively long times, pointing at thermodynamic equilibrium and structural coherency of the interactions.

Such results shall prove the first probe theorizing that certain non-psychomim.

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Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Ethical approval: Not applicable.

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