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Full Paper

Potential human protein targets of cannabidiol revealed by computer-aided structural analysis

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Abstract: Cannabis has been shown to exhibit some therapeutic properties in traditional medicine. However, the molecular insights of its active compound cannabidiol (CBD) remain to be further elucidated. In this study we used bioinformatics approaches to discover potential human protein targets of CBD, how CBD interacts with its putative targets, and its potential pharmaceutical effects. By using a homology approach, we identified 139 human proteins that are homologous to CB1 receptor—the main protein target of CBD. Docking simulations were performed and confirmed on 26 targets, of which 17 were potentially novel. Muscarinic acetylcholine receptor M5 and melatonin receptor type 1B were predicted to have vina scores comparable to the CB1 receptor. These receptors were also shown to be targeted by drugs designed for treating psychological conditions and sleeping disorders. Nonetheless, CBD has a unique structure that was not predicted to be highly similar to other commercial drugs listed on DrugBank. Our in-silico findings provide insights into the binding association between CBD and its putative targets, which could be further studied in vitro and could be of great benefit to clinical researchers in order to utilise cannabis for medical purposes.

Keywords: cannabis, cannabidiol, bioinformatics, drug repurposing, homology

INTRODUCTION

Cannabis sativa is a genus of plants in the family *Cannabaceae*. Its product has been well-regarded as traditional medicine as well as a recreational drug. In Thailand cannabis used to be classified as a narcotic substance under the government's Narcotic Act B.E.2522—it cannot be planted, produced, possessed, sold, imported, exported or consumed. However, it has been recently removed from the list of harmful substances, making it possible to be grown under the allowable amount for household use. If cannabis is not used in moderation, its side effects can be of great concern. According to Thai folk wisdom, cannabis has been used for treating headaches, insomnia, cardiovascular disease, diabetes mellitus and some types of cancer [1]. Despite its traditional

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medical uses, cannabis is yet to be further elucidated for its mechanisms—particularly its binding association with human proteins.

Following Δ^9-tetrahydrocannabinol (THC), which is the most abundant active chemical in cannabis [2], cannabidiol (CBD) is known to be the second most abundant one. Unlike THC, many studies have suggested that CBD lacks psychotomimetic effects [3]. Nevertheless, it was shown to have a wide variety of effects on many clinical conditions such as pain, feeding disorders, multiple sclerosis, glaucoma [4], anxiety, inflammation, neuropathy and epilepsy [5-9]. Both THC and CBD can be transported in blood by albumin or lipoproteins, and intracellularly by fatty acid-binding proteins (FABPs) [10]. A recent study also found that CBD could disrupt cholesterol homeostasis in human cell lines [11]. The various effects of CBD are likely due to its multiple interactions with many protein targets, triggering multiple molecular mechanisms.

CBD (Figure 1A) is known for its ability to bind to several receptors, ion channels and enzymes. According to DrugBank, there were over 70 molecules reported to be targeted by CBD at the time of this study [12]. Yet, the pharmacological actions were still unknown for many of them. CBD was shown to display antagonist properties when bound to its main targets CB1 and CB2 receptors (Figure 1B), which may contribute to its anti-inflammatory properties as previously documented [13].

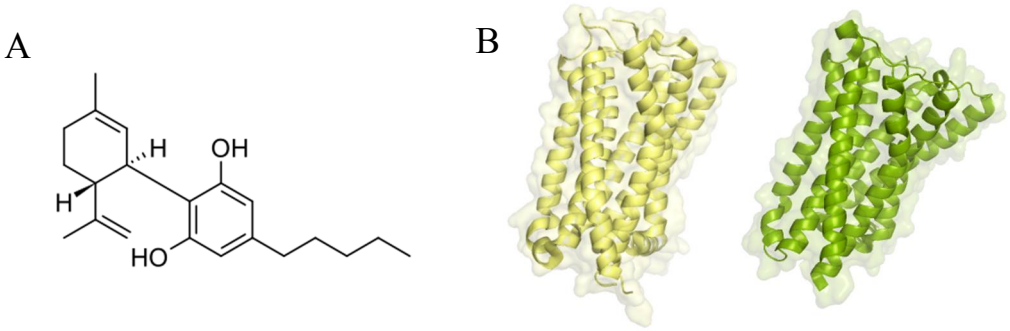

Figure 1. Molecular structures of (A) CBD, (B) CB1 (yellow) and CB2 (green) receptors, two main targets of CBD (Protein Data Bank ID: 5U09 and 5ZTY respectively)

Apart from its two main targets, CBD was known to target a number of G protein-coupled receptors. It was shown to act as an antagonist of GPCR55 [14] and an inverse agonist of GPR3, GPR6 and GPR12 [15]. Being an inverse agonist of GPR3, GPR6 and GPR12 suggests possible therapeutic uses of CBD for neurological disorders such as Alzheimer's disease, Parkinson's disease and other conditions such as cancer and infertility [15]. In addition, evidence suggests that CBD could be beneficial for treating diabetes and cardiovascular diseases [16]. CBD was also shown to inhibit α7-nicotinic acetylcholine (α7 nACh) receptor [17], the receptor that is critical for memory and attention [18] as well as inflammation regulation [19]. Despite its inhibitory or antagonist effects, CBD was proven to be an agonist of many protein receptors including 5-HT1A receptor [20], dopamine D2 receptor [21], adenosine A1 and A2A receptors [22, 23], glycine receptor α1, α1β and α1C subunits [24, 25], and the transient receptor potential cation channel TRPV [26]. Some studies have also suggested the modulatory effects of cannabinoids on opioid receptors (including mu- and delta-opioid receptors) [27, 28] and GABA receptors [29]. The ability of CBD to modulate GABA receptors makes this compound an interesting candidate for conditions such as epilepsy [29]. Other known ion channels that CBD was believed to have inhibitory effects on include calcium channels [30, 31], sodium channels [32] and anion channels [33].

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Most of the widely accepted evidence to explain CBD has been derived from randomised clinical trials, in vitro and in vivo models, as well as observations in the real world. Yet, there are potentially more clinical effects and pharmacological actions of CBD to be discovered as the number of CBD studies has been skyrocketing over the past decade. As CBD has been shown to be able to bind to multiple targets, identifying its potential targets in silico through virtual screening could therefore be a powerful approach to gain more insights into its putative target as well as the potential use of CBD prior to future in vitro and in vivo studies.

It has been well established that proteins that are homologous can share highly conserved and nearly identical active site conformation despite sharing very low sequence identity [34, 35]. Thus, utilising this concept to find out distantly related homologous protein targets of CBD could help researchers uncover new potential protein targets not previously investigated. Similarly, it has been suggested that drugs with similar structures could potentially be repurposed for the treatment of new conditions not previously indicated [36]. Therefore, investigating drugs that share similar structures with CBD could also benefit from this concept and may provide additional insights into the pharmaceutical properties of this natural substance.

In this paper we studied the potential human receptor targets, their binding associations with CBD, and the potential therapeutic properties of CBD using protein homology and drug similarity concept. We used the CB1 receptor as the main query in search of other protein homologues. The binding association between the active compounds and the candidate protein targets was predicted using a web server for molecular docking. The structural comparison of CBD with other modern drug structures found in a drug database was also performed to identify potential indications. This study provides more insights into the structural and molecular basis of CBD using bioinformatic analysis, which could lead to more in vitro or in vivo studies so that clinical researchers can utilise cannabis for medical purposes.

MATERIALS AND METHODS

Retrieval of Cannabidiol and Other Drug Structures

Cannabidiol structure (PubChem ID: 644019) was retrieved from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) [37] in SDF format. Additionally, we retrieved 11,172 drug structures in SDF format from the DrugBank online database (https://go.drugbank.com/) [38]. These structures were used for finding drugs that are structurally similar to cannabidiol.

Identification of Homologous Proteins of Cannabidiol Receptors

To identify putative homologous receptors, the amino acid sequence of the CB1 receptor (extracted from the Protein Data Bank (PDB) structure ID: 5U09) was used in a BLASTP search against the reference protein (refseq_protein) database. The search was limited to human proteins only (taxonomy id: 9606). The maximum number of target sequences was set to 250, and the rest of the parameters were kept at their default settings (expect threshold = 0.05, matrix = BLOSUM62). The protein records that were picked up by the BLASTP search and had complete PDB structures available were then used in docking simulation to confirm their interactions with cannabidiol. Structures that were available partially were not considered. If a protein had multiple PDB structures available, the structure that had the best resolution would be selected.

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Docking Simulation

The docking simulations were performed in receptors of which full (or nearly full) X-ray structures were available in the PDB database. To do so, we used CB-Dock [39], a web server that takes a receptor in PDB format together with a ligand molecule in SDF format as an input. Without the need to identify the binding site, CB-Dock automatically searches for the five largest cavity pockets and attempts to fit the input ligand in the pocket it detects using the AutoDock Vina algorithm [40]. The output of the program includes the simulated docking coordinates in PDB format as well as the vina score and the cavity size where the ligand was fit in. The CB-Dock was reported to have ~70% accuracy [39].

Drug Similarity Comparison

The drug similarity comparison was performed between the cannabidiol structure and the 11,172 DrugBank structures using Tanimoto Similarity Coefficient, which is available in RDKIT python package (version 2021.09.01) (available at www.rdkit.org). The Tanimoto coefficient, ranging from 0 to 1, is calculated as the ratio of the number of elements included in the common structure to the number of elements included in the union of both structures [41]. If the two structures are highly similar, the Tanimoto score will be close to 1.

RESULTS AND DISCUSSION

Potential Targets of CBD by Homology Search

Using the amino acid sequence of the CB1 receptor as the query in the BLASTP search against the reference protein database, we found 139 non-redundant human proteins that are homologous to the CB1 receptor. Many of these targets were isoforms of certain proteins, so the search results could be classified into 32 groups of proteins. The full list of BLASTP search results, the categorisations of the homologues as well as the full analysis results in this study are available at our Harvard Dataverse repository [42]. The majority (93%) of the proteins picked by BLASTP were found to cluster below 30% identities, which was considered too low for them to be regarded as homologous (Figure 2). However, considering the generally high per cent positives (% of similar amino acid components) with 94% having per cent positives of over 40, as well as the E-values (most of which were much below 0.001), it can still be concluded that all of the proteins identified are CB1 homologues. Notably, the lowest per cent identity as detected by BLASTP was 20%, yielded by probable G-protein coupled receptor 27 (NP_061844.1), yet it still had the per cent positive of 42.73, and the E-value was 0.003, suggesting that this protein is a distantly related homologue of the CB1 receptor.

We then searched for high-quality 3D structures of these 139 homologous proteins in Protein Data Bank. However, due to the limited protein structure availability, only 26 homologous receptors were found to have their structures available in Protein Data Bank—9 of these were already experimentally confirmed to be the CBD targets in the previous studies (Table 1), while 17 did not have experimental confirmation in any previous studies, making them candidates to be further investigated (Table 2). These potential CBD targets, along with the confirmed targets, were then used in docking simulations to investigate their binding associations with CBD in silico.

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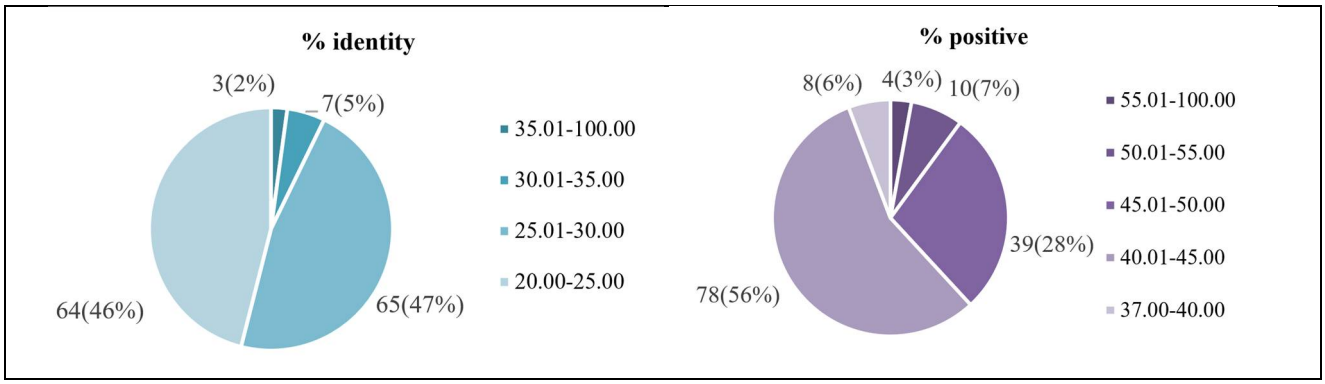

Figure 2. Pie charts showing distributions of 139 human homologues of CB1 receptor as categorised by per cent identities (left) and per cent positives (right)

Table 1. Human homologues of CB1 receptor with available PDB structures and experimental confirmation as targets of CBD in previous studies

Description	Per. ident	Accession	PDB identifier	PDB resolution	Vina score	Cavity size	Ref.
5-hydroxytryptamine receptor 2A	22.39	NP_000612.1	6A94	2.90 Å	−8.4	3256	[43]
adenosine receptor A1	22.87	NP_000665.1	5UEN	3.20 Å	−8.0	2189	[22]
alpha-2A adrenergic receptor	28.26	NP_000672.3	6KUX	2.70 Å	−8.1	5686	[44]
apelin receptor	24.26	NP_005152.1	5VBL	2.60 Å	−8.1	3061	[45]
cannabinoid receptor 1 isoform a	100	NP_001153698.1	5U09	2.60 Å	−8.5	3241	[13]
cannabinoid receptor 2	44.58	NP_001832.1	5ZTY	2.80 Å	−9.3	2408	[13]
D(3) dopamine receptor isoform e	24	NP_387512.3	3PBL	2.89 Å	−6.9	933	[46]
G-protein coupled receptor 52	22.55	NP_005675.3	6LI0	2.20 Å	−7.7	3367	[47]
orexin receptor type 1 isoform X2	26.27	XP_016856596.1	6TOD	2.11 Å	−7.6	4840	[48]

Note:
Per. ident: % identity between CB1 and target protein
Vina score: best docking score (kcal/mol) between target and CBD as predicted by CB-Dock
Cavity size: size of its respective binding pocket (as predicted by CB-Dock)
Ref.: previous studies which confirm binding association between CBD and target

Docking Simulations and Potential Properties of CBD

We first predicted the binding associations between CBD and all the previously confirmed targets listed in Table 1 using CB-Dock. This tool uses AutoDock Vina algorithm which treats receptors as rigid molecules while ligands are treated as flexible. The binding score (here referred to as vina score) is calculated by summing all intermolecular and intramolecular contributions together. These contributions concern mainly hydrophobic interactions, hydrogen bonds, and the distance between atoms in all atom pairs [40]. A more negative vina score indicates a stronger binding affinity (with more hydrophobic interactions and hydrogen bonds created between the ligand and the receptor). The vina scores in Table 1 represent the binding energies (kcal/mol) yielded from docking CBD onto each protein's ligand-binding site. Here, the vina scores range from −6.9 kcal/mol (D(3) dopamine receptor) to −9.3 kcal/mol (cannabinoid receptor 2).

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Table 2. Potential human targets of CBD with available PDB structures

Description	Per. ident	Accession	PDB identifier	PDB resolution	Vina score	Cavity size
5-hydroxytryptamine receptor 1B*	27.41	NP_000854.1	4IAR	2.70 Å	−7.8	1643
beta-1 adrenergic receptor*	24.7	NP_000675.1	7BVQ	2.50 Å	−8.2	1741
cholecystokinin receptor type A	20.94	NP_000721.1	7F8Y	2.50 Å	−7.5	1863
D(1A) dopamine receptor*	24.29	NP_000785.1	7JOZ	3.80 Å	−8.1	885
endothelin receptor type B isoform 1 precursor	23.15	NP_000106.1	6IGK	2.00 Å	−6.4	2293
histamine H1 receptor	30.14	NP_000852.1	3RZE	3.10 Å	−6.7	7260
lysophosphatidic acid receptor 1 isoform a	27.84	NP_001338326.1	4Z35	2.90 Å	−7.3	2414
melanocortin receptor 4	24.93	NP_005903.2	6W25	2.75 Å	−7.7	1068
melatonin receptor type 1B	25.51	NP_005950.1	6ME6	2.80 Å	−8.5	2556
muscarinic acetylcholine receptor M1	34.72	NP_000729.2	6WJC	2.55 Å	−8.5	2199
muscarinic acetylcholine receptor M2	28.77	NP_000730.1	5ZKC	2.30 Å	−8.8	2045
muscarinic acetylcholine receptor M4	28.09	NP_000732.2	5DSG	2.60 Å	−8.5	3678
muscarinic acetylcholine receptor M5	24.83	NP_001307846.1	6OL9	2.54 Å	−8.9	2479
nociceptin receptor isoform 1	22.16	NP_000904.1	5DHG	3.00 Å	−6.5	4089
oxytocin receptor	24.58	NP_000907.2	6TPK	3.20 Å	−7.6	688
sphingosine 1-phosphate receptor 1	31.27	NP_001307659.1	3V2Y	2.80 Å	−7.2	2758
sphingosine 1-phosphate receptor 3	29.8	NP_001382777.1	7C4S	3.20 Å	−7.7	3710

Note:
Per. ident: % identity between CB1 and target protein
Vina score: best docking score (kcal/mol) between target and CBD as predicted by CB-Dock
Cavity size: size of its respective binding pocket (as predicted by CB-Dock)
Receptors that are closely related to those previously confirmed by experiments are marked with *.

Generally, similar binding scores yielded by different receptors could indicate that they have similar binding affinities with CBD. Hence the vina scores yielded by docking CBD to their already-confirmed targets in Table 1 could be used as reference scores in the assessments of the vina scores yielded by docking CBD to their potential targets listed in Table 2. If the vina scores yielded by the unconfirmed targets are at least similar to, or better than, the score yielded by the experimentally confirmed targets, it can be inferred with more confidence that CBD will have a comparatively strong binding association with such targets.

Among the experimentally confirmed targets, the strongest binding associations were observed when docking CBD to cannabinoid receptors 1 and 2 (vina scores: −8.5 and −9.3 kcal/mol respectively). Figure 3A shows the docking result between CBD and the CB1 receptor (PDB ID: 5U09). The original 3D structure 5U09 also contains a drug molecule Taranabant (DrugBank ID: DB06624, Ligand ID: 7DY), which is currently under investigation for treatment in obesity. It can be observed that the predicted binding location of CBD is at the same binding pocket as the Taranabant molecule, confirming a successful docking simulation at the receptor binding site.

When the docking simulation was repeated on each of the candidate targets listed in Table 2, the binding associations could be predicted and similar vina scores were observed. The result indicates that these homologous receptors, especially those with strong vina scores, have the potential to be the binding targets of CBD whether they act as agonists or antagonists, and thus,

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further laboratory experiments should be conducted to verify our in-silico findings (see Figures 4, 5 for all docking results on both confirmed and potential targets).

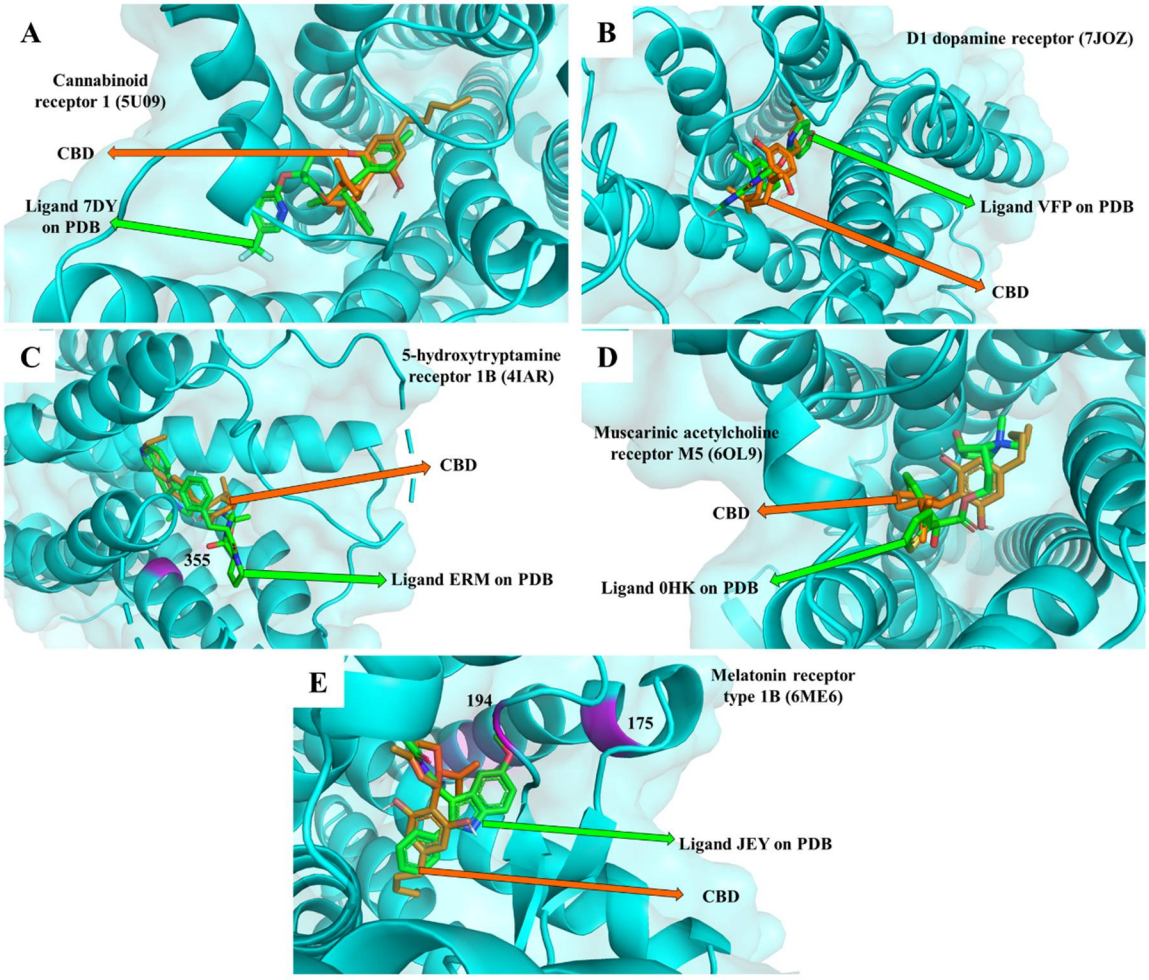

Figure 3. Selected docking results of CBD and its targets: (A) cannabinoid receptor 1, (B) D1 dopamine receptor, (C) 5-hydroxytryptamine receptor 1B, (D) muscarinic acetylcholine receptor M5 and (E) melatonin receptor type 1B. Residues that function as binding sites (as indicated in UniProt) are labelled and highlighted in magenta.

Some of the candidate targets are highly similar to those identified in previous studies. For example, in this paper we identified D(1A) dopamine receptor, with a vina score of −8.1 kcal/mol when bound to CBD (Figure 3B). Indeed, the CBD was predicted to bind to the same pocket as the ligand VFP (6-{4-[(furo[3,2-c]pyridin-4-yl)oxy]-2-methylphenyl}-1,5-dimethylpyrimidine-2,4(1H, 3H)-dione) that originally comes with the PDB structure. Previously, CBD was experimentally confirmed to have a partial agonist effect on dopamine D2 receptors [21]. An additional study has suggested that, when compared to D2 receptors, CBD might have a stronger binding affinity with D3 dopamine receptor, and it is also likely to act as a partial agonist [46]. Although the dopamine receptors are classified as G-protein coupled receptors, both D2 and D3 receptors belong to D2-like family, whereas D1 receptor belongs to D1-like family. Notably, in this study the D1 receptor showed a stronger binding affinity to CBD than the D3 receptor (−8.1 vs −6.9 kcal/mol). This indicates that the molecular effects of the binding between CBD and D1 receptor should be further elucidated through laboratory experiments.

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In addition, we were also able to predict the binding association between CBD and 5-hydroxytryptamine receptor 1B (5-HT1B) (vina score: −7.8 kcal/mol) (Figure 3C), with the CBD predicted to bind to the same pocket as ergotamine (ID: ERM), the drug approved for the treatment of migraine disorders [49]. It has been well established that 5-HT1A is one of the many targets of CBD [20]. In this study we also successfully docked CBD to another confirmed receptor 5-HT2A (vina score: −8.4 kcal/mol), which is known to be the target of serotonergic psychedelic drugs such as lysergic acid diethylamide (LSD) [50]. Although the vina score yielded by 5-HT1B was relatively weaker than that yielded by 5-HT2A, the docking result suggests that the binding between CBD and 5-HT1B is worth further investigation in vitro.

Some novel targets worth mentioning are muscarinic acetylcholine receptor M5 (CHRM5) which had a binding score of −8.9 kcal/mol (Figure 3D) and melatonin receptor type 1B (MTNR1B) (−8.5 kcal/mol) (Figure 3E). In both cases CBD could be predicted to bind to the same pocket as the drugs found in the original PDB structures, suggesting promising binding associations and the possibility of CBD affecting the functionalities of those targets. Muscarinic acetylcholine receptors are acetylcholine receptors in the cell membranes of neurons and other cells in the central and peripheral nervous systems [51]. Muscarinic acetylcholine receptors are also known to be involved in the processes of physiological disorders such as Alzheimer's disease [52]. Our docking simulation shows that CBD can bind very similarly to the approved drug Tiotropium (DrugBank ID: DB01409 Ligand ID: 0HK) (as originally appeared in the PDB structure). Tiotropium is an antimuscarinic bronchodilator used in the treatment of asthma and chronic obstructive pulmonary disease. Thus, more studies should be conducted to elucidate the effect of CBD on CHRM5 as well as its homologues M1, M2 and M4. The functions of melatonin receptors were well known for sleep promotion and the synchrony of biological clocks [53]. According to our docking result, CBD could also bind to MTNR1B, similarly to the original ligand 2-phenylmelatonin (Ligand ID: JEY) which is a melatonin agonist. The strong binding energy between CBD and MTNR1B indicates potential for future experimental studies of utilising CBD in sleep management.

Unconfirmed targets that were predicted to have relatively weaker vina scores but still stronger than the experimentally confirmed D(3) dopamine receptor (−6.9 kcal/mol) were cholecystokinin receptor type A (−7.5 kcal/mol), lysophosphatidic acid receptor 1 (−7.3 kcal/mol), melanocortin receptor 4 (−7.7 kcal/mol), oxytocin receptor (−7.6 kcal/mol), and sphingosine 1-phosphate receptors 1 and 2 (−7.7 and −7.2 kcal/mol respectively). All of them are G-protein coupled receptors under different subfamilies and therefore have different binding partners. Three other unconfirmed receptors which had the weakest binding scores were endothelin receptor type B (−6.4 kcal/mol), histamine H1 receptor (−6.7 kcal/mol), and nociceptin receptor (−6.5 kcal/mol). It can be noticed, however, that when a prediction showed a strong vina score, the CDB molecule tended to be placed at the same binding pockets as the original ligands that come with the PDB structures, and it could be misplaced in some of the targets, especially when the vina scores were not strong (e.g. histamine H1, melanocortin receptor 4 and sphingosine 1-phosphate receptor 1) (see Figure 5). The reason why in some structures CBD was not placed at the supposed binding pockets is due to the CB-Dock's algorithm of finding the location where the best vina score could be yielded. It could also be because the molecular complementarity at the ligand binding site was not ideal. Nevertheless, CD-Dock was shown to have about 70% accuracy [39]. Therefore, prediction errors could be taken into consideration and using other docking analysis tools could be an option to help validate the results.

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This study addresses potential human receptor targets of CBD using homology-based analysis. A certain limitation of this technique is that it only identifies proteins that are evolutionarily related to CB1 receptor—the identified targets are mainly sub-classes of G-protein coupled receptors. Remarkably, there are still many more proteins, transporters, as well as ion channels that could be targeted by CBD, yet they belong to different protein families when compared to the CB1 receptor. Therefore, expanding the search through finding homologous proteins in other families of receptors could also help researchers identify new potential targets of CBD. A recent study using a network-based analysis technique has identified several new potential targets of CBD including catalase, cytochrome P450 family 17 subfamily A member 1, AKT serine/threonine kinase 1, caspase 9, protein kinase C alpha, and tumour necrosis factor [54]. None of these targets shares a high % sequence identity with the CB1 receptor; hence the reason why they were not detected through the BLASTP search in our study. This also suggests that there are many more potential targets of CBD to be discovered through different techniques.

Overall, the docking simulations in this study have revealed potential targets of CBD as well as biological conditions under which it might have effects on. However, in vitro and in vivo validations are still needed. Importantly, in order to ensure the safety and efficacy of CBD when used in medical treatments, further laboratory studies should also cover the toxicity of the substance as it was demonstrated that a high dose of CBD may increase the risk of liver damage due to cholesterol homeostasis in certain types of cells being disrupted [11].

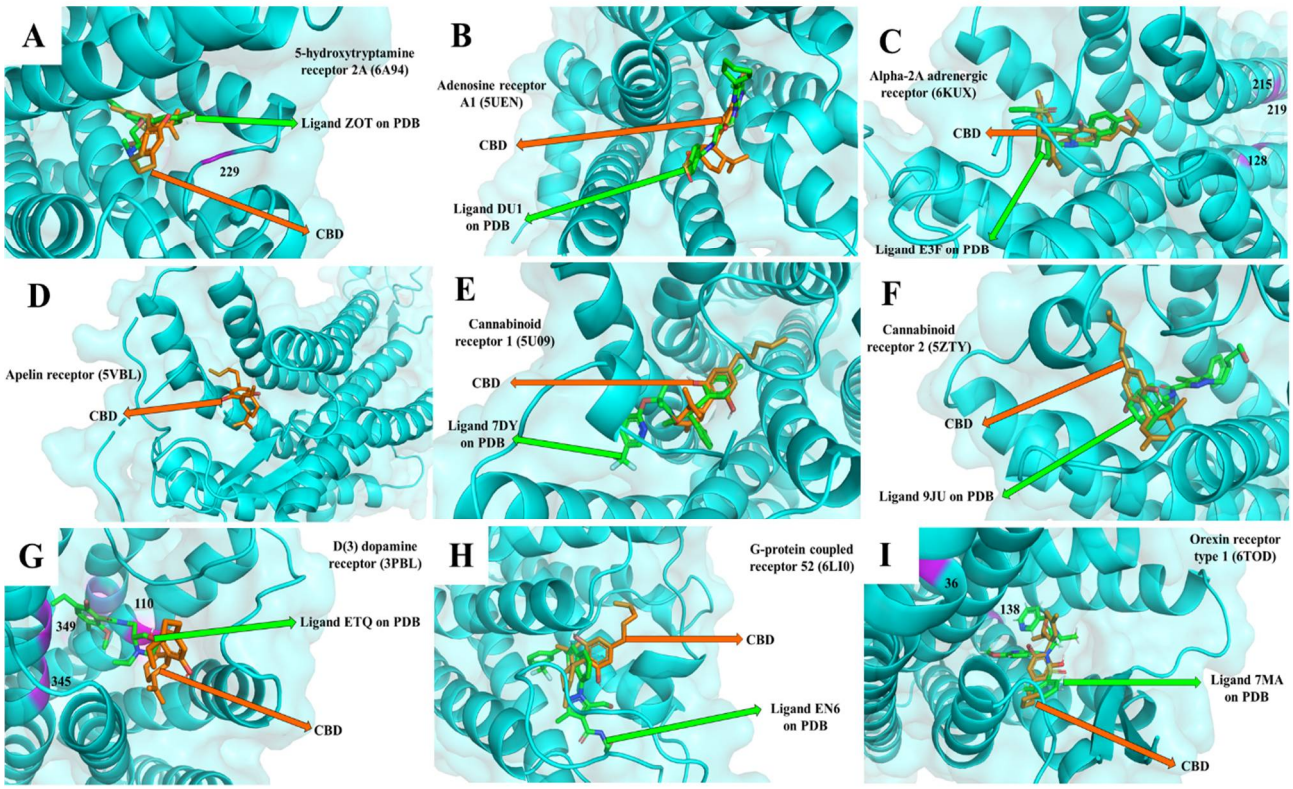

Figure 4. Docking results of CBD and all of its confirmed targets identified in Table 1: (A) 5-hydroxytryptamine receptor 2A, (B) adenosine receptor A1, (C) alpha-2A adrenergic receptor, (D) apelin receptor, (E) cannabinoid receptor 1, (F) cannabinoid receptor 2, (G) D(3) dopamine receptor, (H) G-protein coupled receptor 52, and (I) orexin receptor type 1. The dockings are shown at the locations where the best vina scores were yielded. Residues that function as binding sites (as indicated in UniProt) are labelled and highlighted in magenta.

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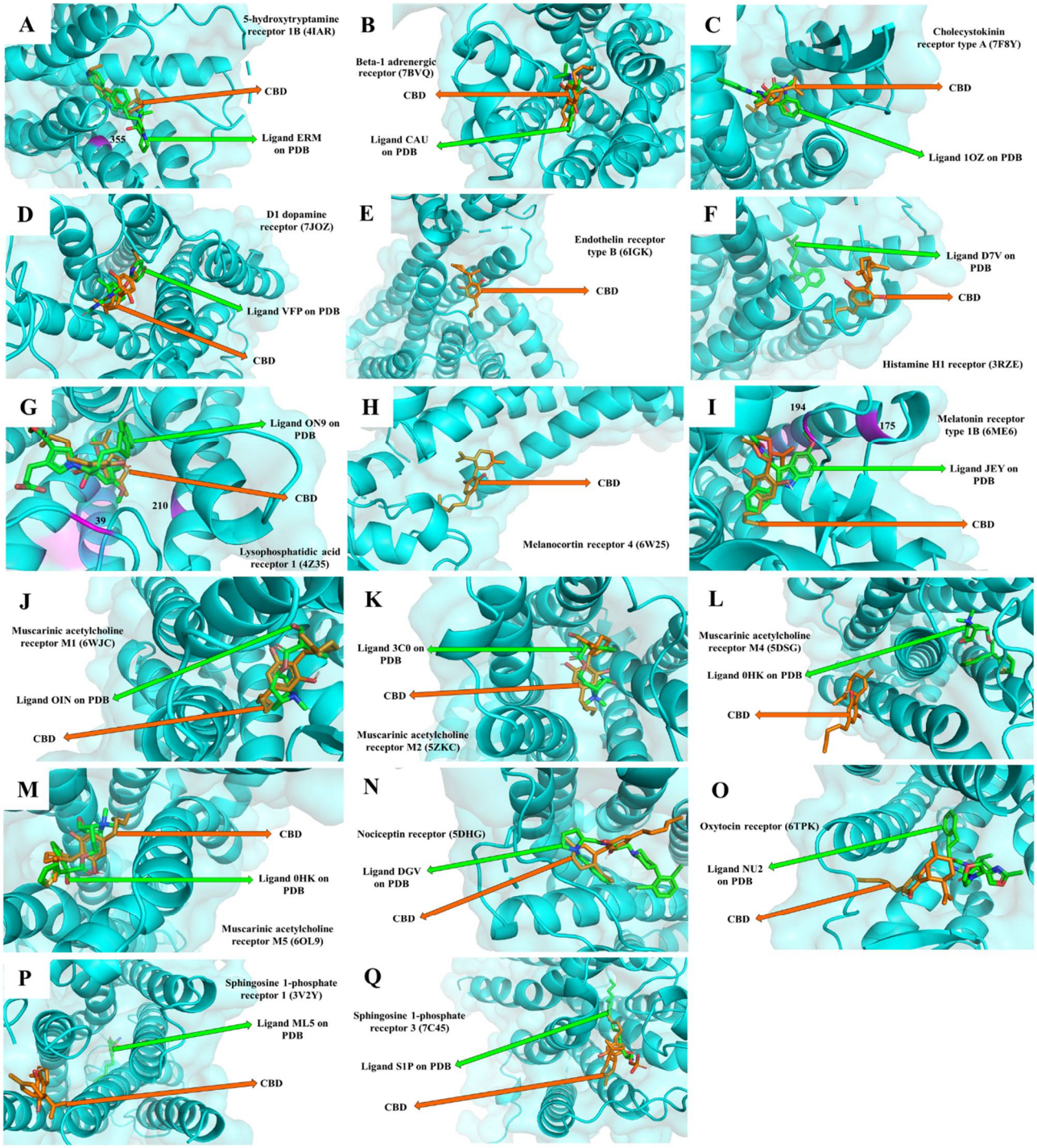

Figure 5. Docking results of CBD and all of its potential targets identified in Table 2: (A) 5-hydroxytryptamine receptor 1B, (B) beta-1 adrenergic receptor, (C) cholecystokinin receptor type A, (D) D1 dopamine receptor, (E) endothelin receptor type B, (F) histamine H1 receptor, (G) lysophosphatidic acid receptor 1, (H) melanocortin receptor 4, (I) melatonin receptor type 1B, (J) muscarinic acetylcholine receptor M1, (K) muscarinic acetylcholine receptor M2, (L) muscarinic acetylcholine receptor M4, (M) muscarinic acetylcholine receptor M5, (N) nociceptin receptor, (O) oxytocin receptor, (P) sphingosine 1-phosphate receptor 1 and (Q) sphingosine 1-phosphate receptor. The dockings are shown at the locations where the best vina scores were yielded. Residues that function as binding sites (as indicated in UniProt) are labelled and highlighted in magenta.

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Similar Drugs to Cannabidiol

A total of 11,160 drugs in DrugBank could be successfully compared to the CBD molecule. However, apart from cannabidiol itself and cannabidivarin (a non-psychoactive cannabinoid and homologue of cannabidiol), none of the drugs in DrugBank yield a high Tanimoto Coefficient. Table 3 shows the top 10 DrugBank molecules that share the highest Tanimoto Coefficient with CBD. The Tanimoto Coefficient should in general be over 0.85 for two drugs to share similar activities [55]. However, the highest similarity is 0.65, yielded by nabiximols, followed by dronabinol (0.59), tetrahydrocannabivarin (0.59), cannabigerol (0.53) and dexanabinol (0.52) respectively. Only xibornol is not considered a cannabinoid molecule. This molecule is a lipophilic drug for the treatment of local infection and inflammation of the throat [56]. However, with its Tanimoto Coefficient of 0.47, which is far below the recommended threshold, this drug may not practically share similar activities to CBD. The result indicates that CBD has a unique molecular structure that hardly resembles other drug molecules, even when compared to other compounds in the cannabinoid family.

Table 3. Top 10 DrugBank molecules sharing highest Tanimoto Coefficients with CBD

Drug Name	DrugBank ID	Cannabinoid	DrugBank Group	Tanimoto Coefficient
Cannabidiol	DB09061	Yes	approved, investigational	1
Cannabidivarin	DB14050	Yes	investigational	1
Nabiximols	DB14011	Yes	investigational	0.65
Dronabinol	DB00470	Yes (synthetic)	approved, illicit	0.59
Tetrahydrocannabivarin	DB11755	Yes	investigational	0.59
Cannabigerol	DB14734	Yes	experimental	0.53
Dexanabinol	DB06444	Yes (synthetic)	investigational	0.52
Ajulemic acid	DB12193	Yes (synthetic)	investigational	0.49
Xibornol	DB13714	No	experimental	0.47
Cannabinor	DB05048	Yes (synthetic)	investigational	0.46

CONCLUSIONS

In this study we have explored the molecular and pharmaceutical properties of CBD using bioinformatic approaches. Several new potential CBD targets have been identified; in-silico docking simulations were achieved on 26 targets whose structures are available, nine of which are experimentally proven. Potential CBD targets include CHRM5 and MTNR1B, which have relatively strong vina scores and are also shown to be drug targets for psychological conditions and sleeping disorders respectively. This in-silico study highlights potential targets that could be further studied in vitro and in vivo. A comprehensive understanding of CBD could give numerous benefits for utilising cannabis in medical applications.

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