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Original Article

In Silico Investigation of the Effect of Cannabidiolic Acid (CBDA) on Muscarinic Acetylcholine Receptors by Molecular Docking Method

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Abstract

Introduction: *Cannabis sativa* contains phytocannabinoids with therapeutic potential for various diseases. Cannabidiolic acid (CBDA), such as phytocannabinoid, has demonstrated antiemetic effects. Postoperative nausea and vomiting are common complications often mediated by muscarinic acetylcholine receptors (mAChRs) in the vomiting center of the brain. This study aimed to investigate the antiemetic effects of CBDA on mAChRs using in silico methods.

Methods: The molecular structure of CBDA was obtained from the PubChem database. Molecular docking simulations with mAChRs were performed using the AutoDock Vina program. Docking results were visualized and analyzed with the Discovery Studio Visualizer software. N – [methyl – 3 H]scopolamine (NMS), a known muscarinic receptor antagonist, was used as a reference drug for comparison.

Results: CBDA demonstrated strong binding affinity with mAChRs, particularly M1 and M3, through significant hydrogen and hydrophobic interactions. Compared to the reference drug NMS, CBDA exhibited significant binding affinity to the receptors, suggesting possible biological activities.

Conclusions: CBDA demonstrated comparable binding affinities to NMS, indicating its potential as a candidate for further antiemetic research. CBDA demonstrated comparable binding affinities to NMS, suggesting that it may have potential for antiemetic applications. However, further studies are needed to clarify its mechanism of action and clinical relevance. Also, its binding profile suggests potential for antiemetic applications, pending functional confirmation. Further in vitro and in vivo studies are required to validate these findings.

Keywords: Antiemetic, *Cannabis sativa*, in-silico, cannabidiolic acid (CBDA), molecular docking

1. Introduction

Emesis, commonly referred to as vomiting, is a distressing physiological response characterized by the forceful expulsion of gastric contents through the mouth. It is primarily associated with gastrointestinal motor functions and serves as a protective mechanism against harmful substances, illnesses, or pharmacological agents (1). The etiology of vomiting is diverse, encompassing food poisoning, motion sickness, gastroenteritis, intestinal obstructions, head trauma, pregnancy, appendicitis, and alcohol-related hangovers. Furthermore, it can arise as a secondary effect of various medical conditions and treatments, including brain tumors, excessive exposure to ionizing radiation, increased intracranial pressure, chemotherapy and radiotherapy (2,3).

The process of emesis is orchestrated by intricate neural mechanisms, with the brain's vomiting center (VC) playing a central role in initiating nausea and vomiting (4). This center is located within the chemoreceptor trigger zone (CTZ) of the fourth ventricle. In addition to the CTZ, multiple regions such as the gastrointestinal (GI) tract, higher cortical centers, vestibular system, and thalamus contribute to the vomiting reflex. The activation of specific proteins within the VC is crucial for triggering this response (5). During emesis, the gastric muscles relax, hydrochloric acid (HCl) secretion is suppressed, and retrograde contractions of the small intestine generate pressure on the stomach, leading to retching and eventual expulsion of gastric contents (6).

The identification of natural sources for novel antiemetic agents remains an area of active research. Several bioactive compounds, including flavonoids, cannabinoids, chalcones, glycosides, hydroxycinnamic acids, diarylheptanoids, lignans, phenylpropanoids, saponins, polysaccharides, and terpenes, have been investigated for their potential in emesis control (7). Among these, *Cannabis sativa* (*C. sativa)* has gained considerable attention due to its historical and contemporary applications in medicine, textiles, and food industries. Phytocannabinoids such as cannabidiol (CBD) and cannabidiolic acid (CBDA) have demonstrated significant antiemetic effects, particularly in the management of chemotherapy-induced nausea, chronic pain, and inflammation (8,9).

Recent studies highlight the therapeutic potential of *C. sativa* derivatives in overcoming the limitations of conventional antiemetic treatments. CBDA exhibits promising interactions with muscarinic acetylcholine receptors (mAChRs), suggesting the potential to prevent the emesis response by inhibiting the receptors. However, further studies are required to fully elucidate its mechanisms of action, optimize pharmacological applications, and ensure its clinical safety and efficacy (10,11).

Beyond its antiemetic properties, *C. sativa* has been reported to alleviate chronic pain and muscle spasms, enhance appetite in individuals with HIV/AIDS, improve sleep quality, and reduce tics in patients with Tourette syndrome. Among its bioactive constituents, phytocannabinoids are recognized as the most potent and pharmacologically relevant components (12). One of the primary targets of antiemetic drugs is the mAChR system.

Muscarinic acetylcholine receptors (mAChRs) belong to the G-protein-coupled receptor family and regulate critical functions within the central and peripheral nervous systems. Acetylcholine (ACh), the endogenous ligand for these receptors, facilitates neurotransmission via both ligand-gated ion channels (nicotinic receptors) and G-protein-coupled mAChRs (13). These receptors are classified into five subtypes (M1–M5), which exhibit distinct expression patterns across various brain regions and peripheral organs (14). Among these, M1, M3, and M5 couple with Gq/11 family G-proteins, while M2 and M4 preferentially interact with Gi/o proteins. Each subtype mediates unique physiological responses, such as synaptic plasticity (M1), gastric acid secretion and smooth muscle contraction (M3), and neurological modulation via dopaminergic and glutamatergic pathways (M4) (15,16).

M2 and M4 receptors primarily function through Gi/o proteins, leading to reduced cyclic adenosine monophosphate (cAMP) levels and subsequent inhibitory effects on cellular signaling (13). These receptors are crucial in regulating cardiac function (M2) and modulating neurotransmitter release (M4),

influencing both autonomic and central nervous system functions (17). The intricate signaling pathways mediated by mAChRs underscore their significance in physiological processes, particularly in the modulation of gastrointestinal motility and nausea. In conclusion, the inhibition of mAChRs presents a therapeutic potential for the development of antiemetic drugs (11).

The precise roles of mAChR subtypes in nausea and vomiting have not been fully elucidated; consequently, currently available mAChR inhibitors lack subtype selectivity in clinical applications. Current anticholinergic drugs, such as N-methyl scopolamine (NMS), lack selectivity among the M1–M5 subtypes, leading to undesirable side effects such as dry mouth, visual disturbances, and drowsiness (17). Therefore, it is of great significance to investigate each mAChR subtype individually to enhance drug selectivity. This study aimed to evaluate the potential inhibitory effect of each mAChR subtype (M1–M5) on emesis through molecular docking with CBDA using *in silico* methodologies.

2. Methods

The pharmacological properties of the compound were determined using SwissADME, a freely accessible web-based tool for estimating ADME parameters. The SMILES form of the CBDA molecule was taken from PubChem and entered into the SwissADME web tool, and the results were obtained.

2.1. Target protein and ligand preparation

The three-dimensional (3D) structure of the M1, M2, M3, M4 and M5 target proteins were taken from the RCSB PDB. M1-5 crystallographic structures with PDB identity 6WJC(M1) (Resolution: 2.55 Å), 5ZK8(M2) (Resolution: 3.00Å), 4U15(M3) (Resolution: 2.80 Å), 5DSG(M4)(Resolution: 2.60 Å) 6OL9(M5) (Resolution: 2.54 Å) were used. In the BIOVIA Discovery Studio 2021 program, unnecessary residues such as water other than the protein in the receptor obtained from the PDB, were removed from the structure. Energy minimization was carried out to obtain a stable conformation. The structure of the selected ligand, CBDA (PubChem ID: 160570), was obtained from the PubChem chemical compounds database (accessed 17.06.2023) The protein's 3D structure and polarization image were obtained using the PyMOL tool.

2.2. Molecular docking

In the study, the AutoDock Vina tool (version 1.5.7) was used to investigate the molecular interaction between target proteins and the selected ligand. Before docking analysis, the structure of the enzyme was optimized using the BIOVIA Discovery Studio 2021 program. Then all compounds were optimized for energy using the Spartan 14 (Version 1.1.4) program. Polar hydrogens were added to the protein using the AutoDock vina 1.5.7 tool, and Kollman charges were determined as partial charge of compounds calculated using Compute Gasteiger. BIOVIA Discovery was used to determine the active sites of proteins. The x, y, and z coordinates were determined to bind the proteins to the catalytic site. After protein and ligand preparation in Autodock Vina, a grid box was generated.

Target proteins grid box values; for M1 x = 20.4468 y = 13.5360 z = 2.5246 (size:90.00), for M2 :x = 184.1934 y = 27.8428z = 526.0209 (size:62.00) for M3 :x = 25.0037 y = 91.8625 z = 53.4823(size:90.00), for M4: x = 51.6869 y = – 1.0918 z = 79.0402 (size: 90.00), for M5 :x = 35.3866 y = 21.7023 z = – 42.8548 (size 60.00) .

Finally, molecular interactions and binding types between the selected compound and target protein were investigated by using the Discovery Studio visualizer program.

3. Results and Discussion

3.1. 3D Prediction of target proteins

In order to attain a comprehensive understanding of the 3D structure of the target proteins, the 3D conformation and surface electrostatic potential representation of the target protein were derived utilizing the PyMOL software. Determining the surface electrostatic potential map of the receptors is crucial for confirming that the ligand is correctly positioned in the binding pocket after the interaction.

Surface electrostatic potential elucidates the distribution of charges present on the protein surfaces. Regions depicted in blue signify the presence of positive charges, areas depicted in red indicate negative charges, and regions depicted in white denote neutral charges. It is observed that the distribution of negative and positive charges is homogeneously allocated across the surfaces of the M1, M3, and M4 proteins. In contrast, in the M2 and M5 proteins, positive charges are notably concentrated in the central region of the protein, whereas neutral and negative charges demonstrate a more pronounced presence at the termini of the protein. As a result of examining the polarization maps, binding pockets (grid boxes) for proteins were determined (Table 1).

Table 1. 3D structure and polarization image of target proteins.

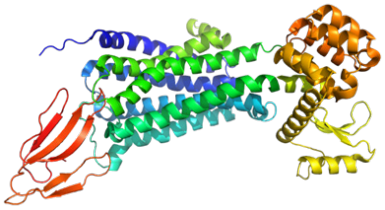
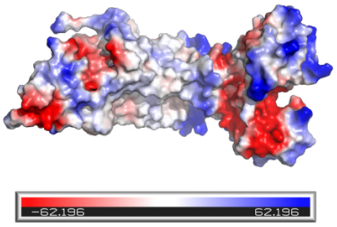
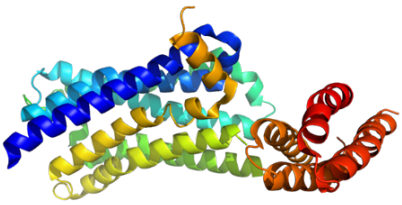
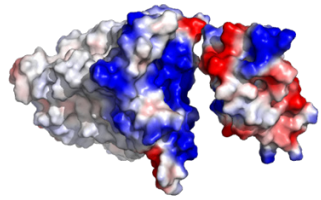
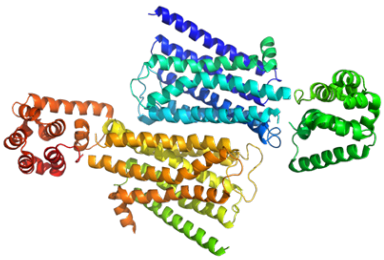
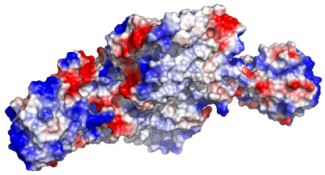
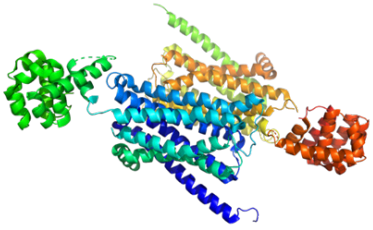
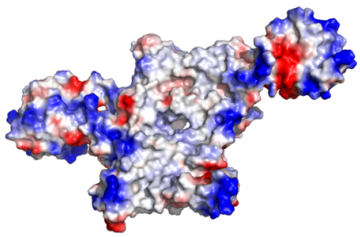
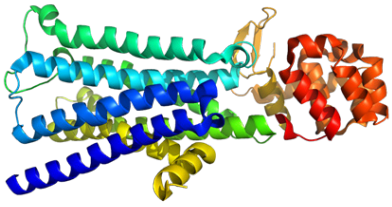
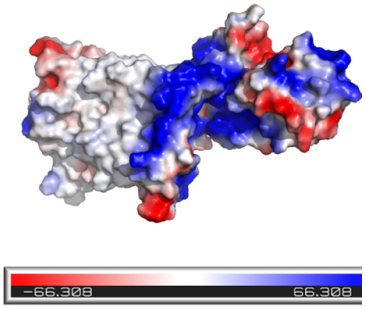
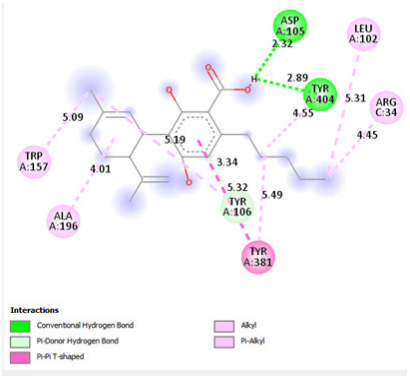
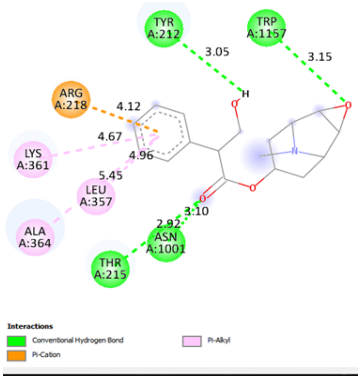
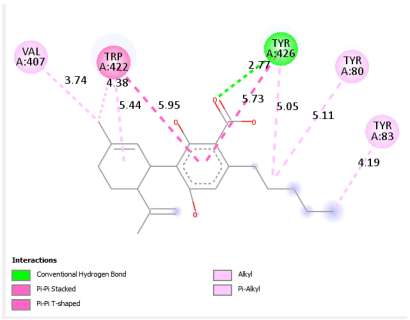
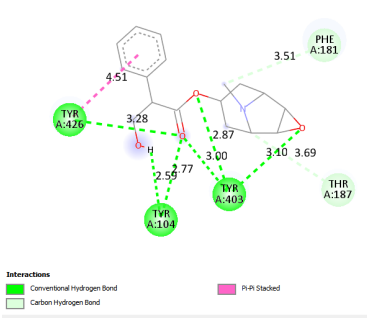
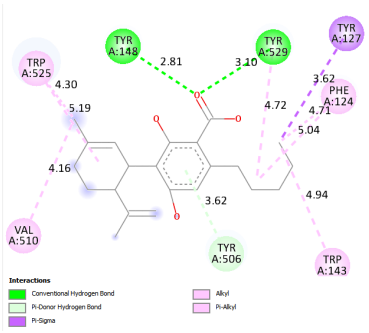
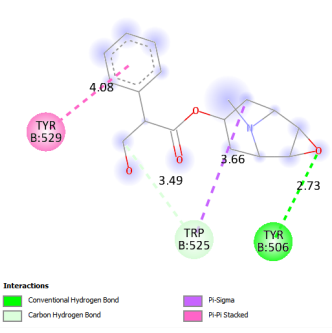
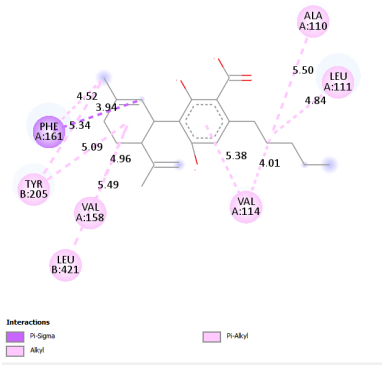
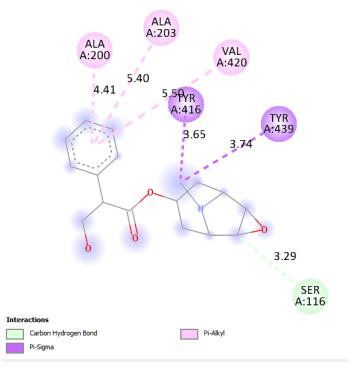
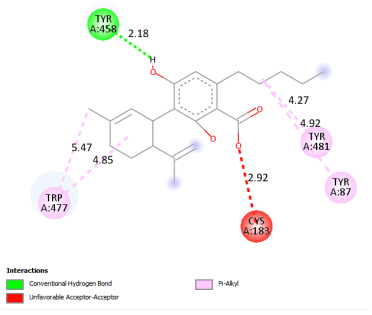
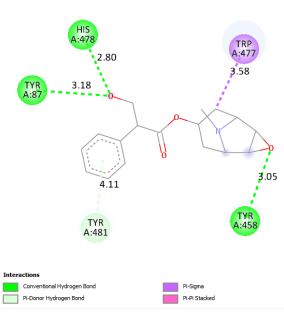
Target protein	3D structure	Polarization image
M1 (6WJC)		
M2 (5ZK8)		
M3 (4U15)		
M4 (5DSG)		
M5 (6OL9)		

Table 2. Interactions of ligands with target proteins.

Target Proteins	CBDA	NMS
M1		
M2		
M3		
M4		
M5		

To assess the reliability and accuracy of the docking protocol employed in this study, a redocking procedure was conducted using NMS, a well-characterized muscarinic receptor antagonist (Table 2). The ligand was redocked into the binding sites of the M2 (PDB ID: 3UON) and M3 (PDB ID: 4DAJ) mAChR crystal structures. The predicted binding poses were compared to the experimentally observed co-crystallized ligand conformations, and the root-mean-square deviation (RMSD) values were calculated. The RMSD values are obtained 0.580 Å for the M2 receptor and 1.339 Å for the M3 receptor, indicating that the docking protocol could reliably reproduce the experimentally determined ligand orientations within an acceptable threshold (RMSD < 2.0 Å).

3.2. Pharmacological properties of CBDA

Results of bioavailability radar, including the chemical structure of the molecule and lipophilicity, size, polarity, solubility, saturation, and flexibility properties, were found on the SwissADME web server (Fig 1). The Log S (ESOL) value of CBDA is – 5.93, classifying it as moderately soluble, whereas NMS has a Log S value of – 2.21, indicating higher solubility. This suggests that NMS exhibits better aqueous solubility than CBDA. CBDA's lower water solubility may limit its absorption and distribution; however, its higher lipophilicity may enhance membrane permeability, which is advantageous for oral bioavailability. The iLOGP (3.45), XLOGP3 (6.60), and MLOGP (3.79) values of CBDA are higher than those of NMS (2.35, 0.98, and 1.19, respectively), indicating that CBDA is more lipophilic and exhibits greater solubility in lipid environments. Increased lipophilicity can enhance membrane permeability but may concurrently reduce aqueous solubility.

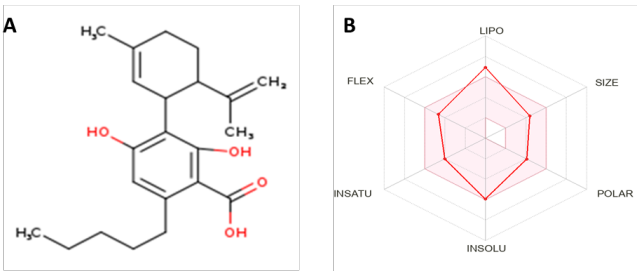


Figure 1. Chemical 2D structure (A) and bioavailability radar of CBDA (B) (19).

Regarding gastrointestinal absorption (GI absorption), both compounds exhibit high absorption rates, suggesting efficient intestinal uptake upon oral administration. In terms of blood-brain barrier (BBB) permeability, SwissADME predictions indicate that neither CBDA nor NMS can cross the BBB. Therefore, the potential antiemetic effects of CBDA might be mediated peripherally. However, these predictions need confirmation through further pharmacokinetic and *in vivo* studies. Although CBDA fulfills drug-likeness criteria such as Lipinski's Rule of Five, its pharmacokinetic profile presents both strengths and limitations. Its high GI absorption and lipophilicity are favorable for oral delivery, but low aqueous solubility and inability to cross the blood-brain barrier (BBB) may restrict systemic or central effects. Therefore, further ADMET profiling, including metabolic stability and bioavailability studies, is needed to support its potential as a therapeutic agent.

Both compounds comply with Lipinski's Rule of Five, with no violations observed. This adherence suggests that they possess favorable oral bioavailability and are suitable candidates for drug development (Table 3) (19).

Table 3. Pharmacokinetic properties of CBDA using the SwissADME web server (18).

Properties	Parameters	CBDA	NMS
Physicochemical Properties	Formula	C22H30O4	C17H21NO4
	MW	358,47 gr/mol	303.35 g/mol
	num. H bond acceptors	7	5
	num. H bond donors	4	1
Lipophilicity	iLOGP	3.45	2.35
	XLOGP3	6.60	0.98
	MLOGP	3.79	1.19
Water Solubility	Log S (ESOL)	-5.93	-2.21
	Class	moderately soluble	Soluble
Pharmacokinetics	GI	high	high
	BBB	No	No
	LogKp	– 3.80 cm/s	-7.45 cm/s
	p – gp substrate	No	No
	CYP1A2 inhibitor	No	No
	CYP2C19 inhibitor	No	No
	CYP2C9 inhibitor	yes	No
	CYP2D6 inhibitor	No	Yes
	CYP3A4 inhibitor	Yes	No
Drug-likeness	Lipinski	Yes; 0 violations	Yes; 0 violation

3.3. Molecular-docking study of the inhibition of M1-5 by CBDA

Nausea and vomiting are triggered by receptors located in the CTZ of the brain. One of these receptors is the mAChR, and the development of inhibitory molecules targeting these receptors is crucial for the treatment of emesis. However, mAChRs are divided into five different subtypes, and M1 and M3 receptor subtypes have been particularly implicated in the emetic response in previous studies. This lack of specificity hinders the development of selective inhibitors, leading to side effects due to non-selective molecular interactions. In this study, the effect of CBDA, which is hypothesized to exhibit inhibitory activity on mAChRs, was investigated for each mAChR subtype using the molecular docking method. The hydrogen, hydrophobic, and other interactions between protein and ligands as a result of the coupling study with the M1-5 receptor with CBDA and reference drug NMS are shown in Table 4.

Table 4. Binding affinity value, hydrogen bonds, hydrophobic and other interactions of mAChRs (M1-5) with CBDA and reference drug.

Target protein	Compound Name	Binding affinity (Kcal/mol)	Hydrogen bonds interactions	Hydrophobic interactions	Others interactions
M1 Receptor interaction	CBDA	– 7.0	ASP105 (2.32Å) TYR404 (2.89Å) TYR106 (3.34Å)	LEU102 (5.31Å) ARG34 (4.45Å) TYR381 (5.49 Å, 5.32Å) TYR106 (5.19Å) ALA196 (4.01Å) TRP157 (5.09 Å)	-
	NMS	-6.1	TYR212 (3.05Å) TRP1157 (3.15Å) ASN1001 (3.10Å) THR215(2.92 Å)	LEU357 (4.96Å) ALA364 (5.45Å) LYS361 (4.67Å)	ARG218 (4.12Å)
M2 Receptor interaction	CBDA	-7.5	TYR426 (2.77Å)	VAL407 (3.74Å) TRP422 (4.38Å, 5.44Å, 5.95Å) TYR426 (5.73Å) TYR80 (5.11Å) TYR83 (4.19Å)	-
	NMS	– 7.4	TYR426 (3.28Å) TYR104 (2.59Å, 2.77Å) TYR403 (3.00Å, 2.87Å, 3.10Å) THR187 (3.69Å) PHE181 (3.51Å)	TYR426 (4.51Å)	-
M3 Receptor interaction	CBDA	-8.0	TYR148 (2.81Å) TYR529 (3.10Å) TYR506 (3.62Å)	TRP525 (4.30Å, 5.19Å) VAL510 (4.16Å) TYR127 (3.62Å) PHE124 (4.71Å, 5.04Å) TRP143 (4.94Å)	-
	NMS	-8.1	TYR506 (2.73Å) TRP525 (3.49Å)	TYR529 (4.08Å) TRP525 (3.66Å)	-
M4 Receptor interaction	CBDA	-8.1	-	PHE161 (3.94Å, 4.52Å) TYR205 (5.09Å, 5.34Å) VAL158 (4.96Å) LEU421 (5.49Å) VAL114 (5.38Å, 4.01Å) LEU111 (4.84Å) ALA110 (5.50Å)	-
	NMS	-8.5	SER116 (3.29Å)	ALA200 (4.41Å) ALA203 (5.40Å) VAL420 (5.50Å) TYR416 (3.65Å) TYR439 (3.74Å)	-
M5 Receptor interaction	CBDA	-7.2	TYR458 (2.18Å)	TYR481(4.27Å) TYR87(4.92Å) TRP477(5.47Å, 4.85Å)	CYS183 (2.92Å)
	NMS	-7.7	TYR458 (3.05Å) TYR87 (3.18Å) HIS478 (2.80Å) TYR481 (4.11Å)	TRP477(3.58Å)	-

In the study, the presence of hydrogen bonds and the binding affinity values expressed with negative values show that a lower value indicates stronger binding compared to the reference drug, thus showing a stronger inhibitory effect.

In the docking study, CBDA was observed to bind well to the M2, M3, M4 and M5 receptors (Fig 2). When compared to the reference drug used in the study, the binding affinity values were found to be remarkably similar. These observed values suggest that CBDA also has the potential to act as a therapeutic agent targeting these receptors. The strong binding of molecules to the receptor indicates effective inhibition of that receptor. Therefore, by suppressing the receptors responsible for initiating nausea and vomiting, the aim is to prevent the onset of these symptoms.

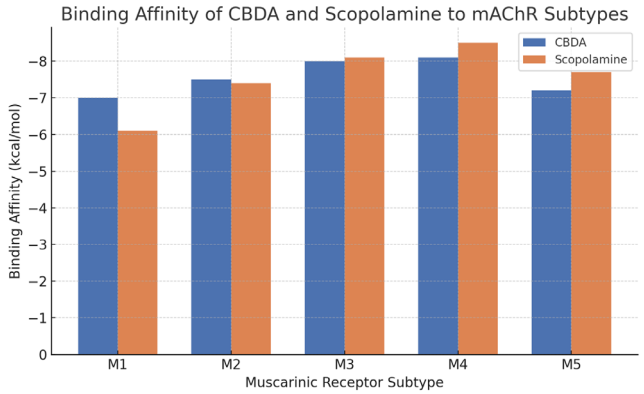


Figure 2. Comparative binding affinities of CBDA and NMS to mAChR subtypes (M1–M5) as predicted by molecular docking. CBDA shows stronger binding to M1 and M4, while NMS exhibits slightly higher affinity for M3 and M5.

At the M1 receptor, CBDA demonstrated a binding affinity of – 7.0 kcal/mol, which is notably higher than that of NMS, measured at – 6.1 kcal/mol. This indicates that CBDA exhibits well receptor binding compared to NMS at this specific receptor. The docking results demonstrated that CBDA exhibited stronger binding affinity to M1, M3, and M4 receptors, particularly M3 and M4. Since M1 and M3 subtypes have been implicated in the emetic reflex, stronger binding to these subtypes may indicate a potential antiemetic effect of CBDA. On the other hand, notable affinity for the M4 receptor, which is involved in dopaminergic and cholinergic modulation, may suggest broader therapeutic implications beyond emesis, possibly in neuropsychiatric or gastrointestinal disorders. Therefore, CBDA's differential binding profile highlights the potential for subtype-selective therapeutic targeting, which could reduce the side effects commonly associated with non-selective muscarinic antagonists like NMS.

In our previous study, the 5HT3A receptor showed a binding affinity of – 7.0 kcal/mol with CBDA (18). Similarly, in the current study, CBDA was observed to form both hydrophobic and hydrogen bonds with mAChRs receptors. When comparing the results, it is difficult to determine which receptor showed better efficacy with CBDA, as the binding affinity values are similar to those of the reference drugs used. Regarding dopamine (D2-D3) receptors, the docking study revealed binding affinities of – 7.8 kcal/mol and – 7.2 kcal/mol, respectively (18). In this study, CBDA was observed to form primarily hydrophobic interactions with both D2 and D3 receptors. Additionally, hydrogen bonds were observed for mAChR receptors, particularly at M1 and M3 receptors. Although these comparisons are not sufficient to definitively determine which receptor CBDA binds to more effectively, they do provide a preliminary basis for further investigation.

In addition, CBDA was observed to form strong hydrogen bonds at M1 and M3 receptors. It was also found to form good hydrophobic interactions between M1–M5 receptors. The effects of CBDA specifically at M1 and M3 receptors may contribute to the development of new treatments for vomiting or other disorders associated with mAChRs.

The binding affinity of CBDA compared to NMS suggests that it may exhibit similar interaction properties. However, functional effects cannot be concluded based on docking results alone. Furthermore, further investigation of factors such as side effects and bioavailability is necessary for clinical application. Additional pharmacokinetic and pharmacodynamic studies should be conducted to advance CBDA into clinical trials.

4. Conclusion

Considering the interactions of CBDA with mAChRs (M1-M5) revealed in this study, CBDA

may exhibit promising binding properties with muscarinic receptors. However, its pharmacological properties await further experimental validation. Molecular dynamics and *in vitro* studies are needed to better evaluate the results obtained in the present study.

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Ethics approval: Not applicable

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