EXPLORING THE PROTEIN-PROTEIN INTERACTIONS AND THE PHYSIOLOGICAL IMPACT OF CANNABINOIDS THROUGH BIOINFORMATICS ANALYSIS

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ABSTRACT

Background: Weed smoking is a vastly unfavorable and perilous practice that can lead to various diseases, but it can also have beneficial effects on the human body. It comprises mainly two bioactive cannabinoids, delta 9-tetrahydrocannabinol and cannabidiol; they have both adverse and beneficial effects on human health. **Objective:** This study aims to identify the proteins interacting with delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) to predict their potential influences on the human body. **Materials and Methods:** We retrieved 200 proteins from the STITCH and STRING databases to analyze the interaction networks (PCI and PPI). We used OmicsBox to perform functional and pathway analysis of proteins associated with these compounds. Furthermore, the Cytoscape networking tool was utilized to identify crucial proteins and their significant pathways. We used Pyrx to assess potential direct interactions between THC and CBD with their associated proteins. **Results:** Functional annotation analysis revealed that THC and CBD interacted with various biological processes of human health, including signaling, anatomical structure development, cell differentiation, DNA binding, oxidoreductase activity, and cytosol activity. Fourteen key proteins were identified based on degree centrality, including ESR1, CREB1, INS, POMC, CNR1, JUN, NTRK2, CYP2B6, PPIG, CYP3A4, CYP1A2, CYP2E1, CYP2C9, and CYP2C19. These proteins play regulatory roles in various Reactome and KEGG pathways. Hypothetical direct interaction analysis showed that THC strongly interacted with pre-prodynorphin protein (-8.5 kcal/mol) and CBD connected with Cytochrome P450 1A1 protein (-8 kcal/mol). **Conclusion:** Therefore, this study contributes to understanding protein interactions and pathways, aiding in the development of drugs targeting CBD- or THC-related changes or associated diseases.

KEYWORDS: PCI, PPI, Delta 9-tetrahydrocannabinol, Cannabidiol, and Functional analysis.

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Introduction

Cannabis, sometimes known as weed or marijuana and with the generic name *Cannabis sativa*, is currently used by more than 3.8% of the worldwide population. It is also used as an unwise drug that affects pre-adult health (Chetia and Borah, 2020). Excessive use of this drug leads to a variety of health problems and may have adverse effects on human health (Cohen *et al.*, 2019; Rahman *et al.*, 2022). On the other hand, this plant has been used since ancient times for its traditional and medicinal impacts on human health, and a fantastic cluster of roughly 540 characteristic chemical compounds has been recognized; among these compounds, around 100 have been recognized for their potential to initiate different physiological impacts and well-being issues in the human body (Amin and Ali, 2019).

Delta 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are two major well-recognized cannabinoids that have drawn significant attention in biomedical science (Abyadeh *et al.*, 2023). THC provides numerous medicinal benefits, including down-regulating inflammatory responses through several pathways, impacting nausea caused by cancer treatment, hunger stimulation, some severe illnesses, neurological symptoms, and

increased markers associated with all phases of neurogenesis (Carlini, 2004; Suliman *et al.*, 2018; Voth, 1997). However, it is a well-recognized psychoactive compound that results in hallucinations and delirium symptoms. THC can also trigger adverse effects, including scattered ideas, anxiety reactions, disconcerting alterations in thinking, illusions, and hallucinogenic sensations. Nonetheless, it may successfully minimize dependence on cannabis in an outpatient environment. Therefore, it is necessary to find out all the proteins and their possible interacting pathways to treat these conditions if overdose or misuse is noticed (Budney *et al.*, 2007). On the other hand, CBD is another key phytochemical that doesn't have psycho-modulatory effects but has beneficial effects such as pain relief, antimicrobial, anti-inflammatory, psycho-protective, and treating epilepsy, nausea, vomiting, seizures, and multiple sclerosis (Lee *et al.*, 2024). However, cannabinoids can also induce some side effects, including inhibition of hepatic drug metabolism, alterations of in vitro cell viability, decreased fertilization capacity, and lessened activities of p-glycoprotein and other drug transporters (Muniyappa *et al.*, 2013).

Protein-protein interaction and analysis of THC and CBD-responsive pathways may help unravel novel approaches and possible drugs to treat many diseases, as they interact with many proteins and receptors, modulating different pathways (Atakan, 2012). These compounds appear as agonists at the prototypical cannabinoid receptors, CB1, CB2, and G protein-coupled receptors that are capable of regulating numerous pathological conditions, including neuropsychological disorders and neurodegenerative illnesses (Dhein, 2020). Moreover, they clinically act as psychoactive operators and have anxiolytic and antipsychotic properties utilized for restorative purposes in a few pharmacokinetics and pharmacological uses associated with neuro-related receptors such as CNR1, CNR2, GPR55, and TRPV2 (Bian *et al.*, 2019). Comprehension of the complex interactions of THC and CBD inside the human body is significant for determining their impacts on the human body (Wilson *et al.*, 2019).

Bioinformatics has long provided essential tools for considering such research. The search tool for interacting chemicals (STITCH) and the search tool for the retrieval of interacting genes/proteins (STRING) databases offer broad stores of chemical-protein and protein-protein interaction systems, encouraging the identification of Cannabis impacts. STITCH is a web server that helps predict the interaction networks between chemicals and proteins of specific species, discovered by experiments and literature mining (Kuhn *et al.*, 2014). STRING is a web server that methodically collects and organizes protein-protein interactions that comprise biological and physical relationships (Szklarczyk *et al.*, 2023). Moreover, Omicsbox is used in different kinds of genomic and proteomic data analysis and also determines the relationship between sequences in biological processes, molecular functions, and cellular components, and identifies the pathways from the different databases, such as KEGG and Reactome (Sheikh *et al.*, 2025). The purpose of this study is to determine the interactions of human proteins with THC and CBD bioactive substances, as well as to reveal their biological, cellular, and molecular roles and the favorable and detrimental impacts of weed smoking.

Materials and Methods

Network retrieval

In this study, two compounds, including THC and CBD, interact with human (*Homo sapiens*) proteins that were retrieved by the Search Tool for Interactions of Chemicals (STITCH) web server followed by Miah *et al.* (2024). THC and CBD interact with human proteins and are further considered to determine the protein-protein interactions, to get all known human protein interactions based on direct (physical) and indirect (functional) associations via the Search Tool for the Retrieval of Interacting Genes (STRING) database.

Sequences collection

The protein sequences in FASTA format were retrieved from the National Center for Biotechnology Information (NCBI) database, and the corresponding amino acid numbers were obtained from the Universal Protein Knowledgebase (UniProtKB) database (Miah *et al.*, 2024).

Functional annotation

OmicsBox 3.2 is a bioinformatics software that analyzes the NGS data of genomes, proteomics, transcriptomes, and metagenomes. It was used to complete the functional annotation of FASTA-format protein sequences (Osman *et al.*, 2023).

Identification of essential proteins and regulated pathways

Cytoscape was utilized to visualize and analyze the protein-protein interaction (PPI) network, following Sheikh *et al.* (2025). Initially, 98 (THC) and 90 (CBD) associated proteins were selected to construct the STRING network in Cytoscape (Figure 1). The top 30 proteins were then identified based on degree centrality using the cytoHubba plugin, while their names were obtained through the STRING tool. Highly central nodes, known as hubs, are marked in red, indicating their critical role in various biological processes, whereas fewer essential nodes are shown in yellow. Finally, the Enrichr database analyzed the significant protein clustergram and key interaction pathways (Reactome and KEGG).

Protein and ligand structures extraction and preparation

We collected 20 protein structures from the AlphaFold protein structure database and the RCSB PDB Protein Data Bank, where 10 targeted proteins were for THC and 10 for CBD. Later, we retrieved the THC and CBD SDF structures from the PubChem Database, and then we formatted the SDF files to PDBQT by PyRx 2.6 while performing molecular docking. The drug properties, such as pharmacokinetics, water solubility, lipophilicity, and physicochemical properties, were verified by SwissADME. In addition, the Lipinski Rule of 5 was determined by using the SCFBio server.

Molecular docking analysis

Molecular docking was conducted by PyRx 2.6 and visualized using BIOVIA Discovery Studio 2024, followed by Dallakyan and Olson (2015).

Results

Collections of human proteins that are associated with THC

THC interacted with 10 human proteins, including CNR1, CNR2, CASP3, FOS, PDYN, GPR55, BDNF, POMC, CYP1B1, and PRL, identified through protein-chemical interactions (PCI). Then, each of these proteins was associated with another 10 proteins; as a result, 100 proteins were obtained from the STRING database by protein-protein interactions (PPI) (Figure 1).

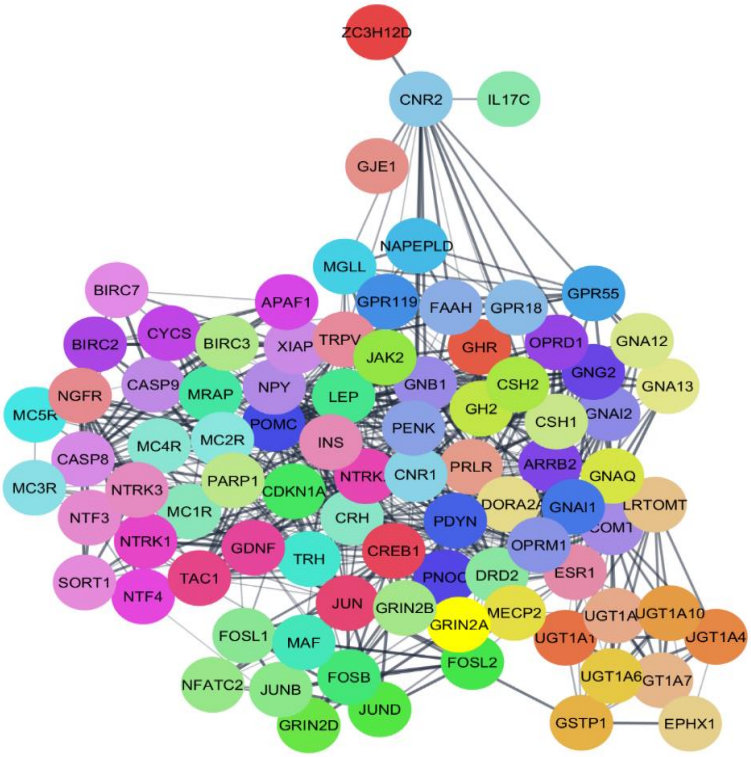
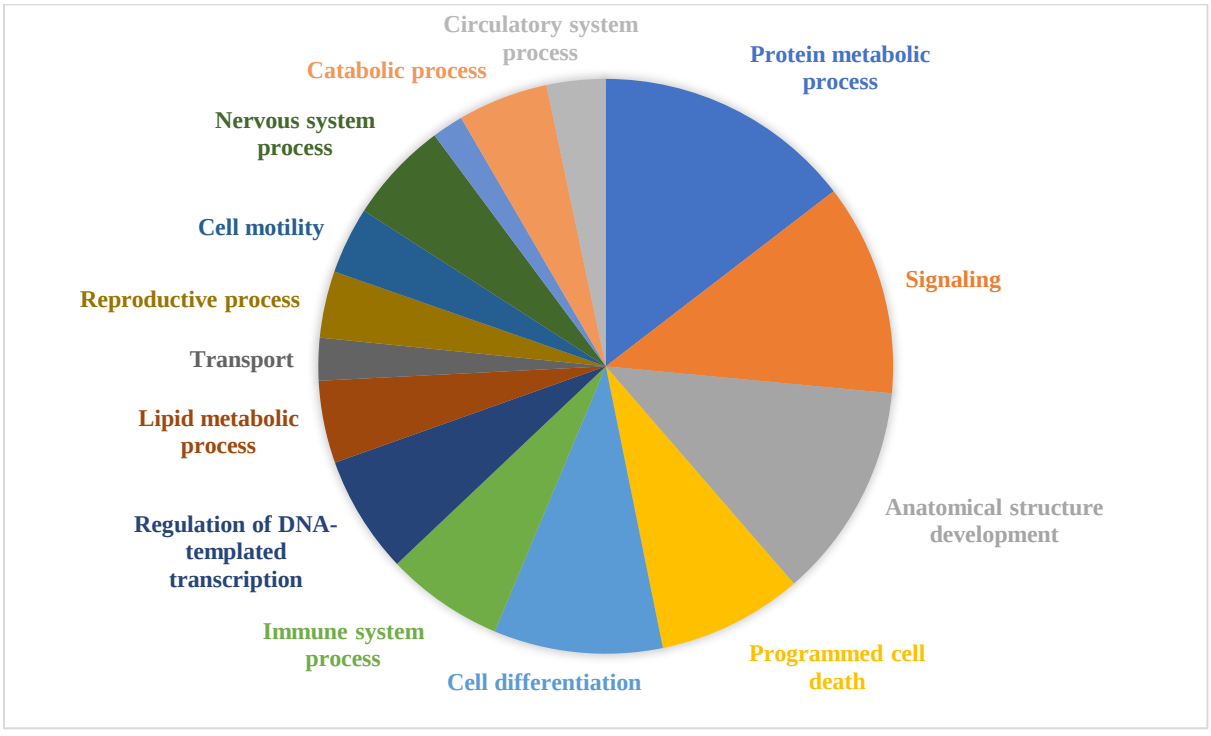


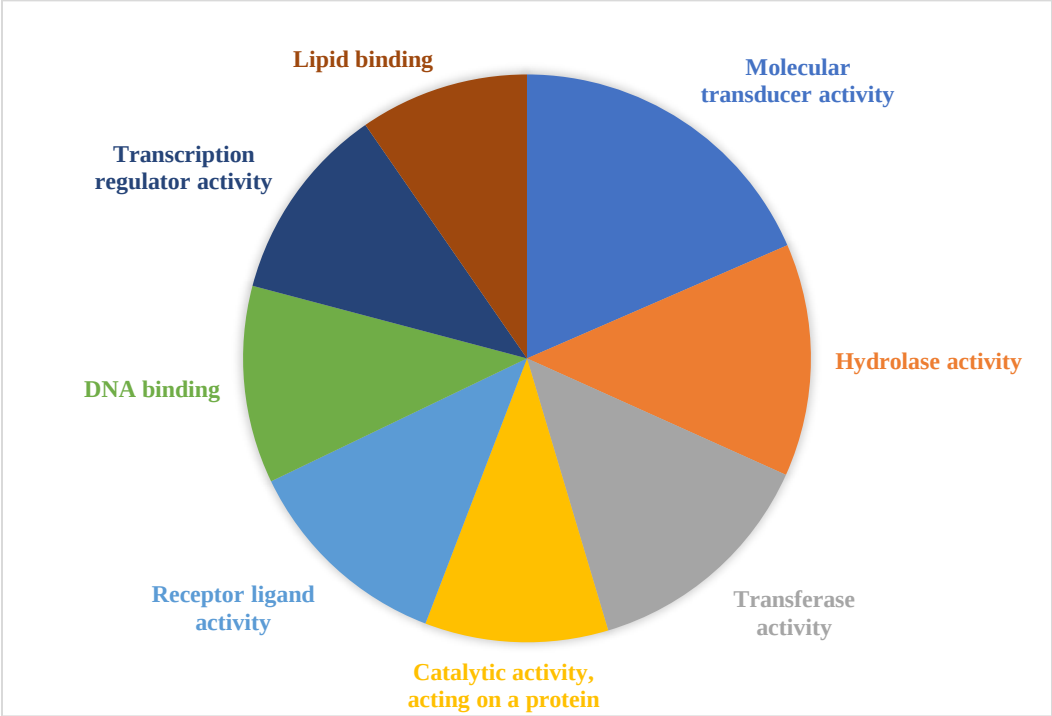
Figure 1. Protein-protein interaction (PPI) of THC identified via STRING 12.0

Functional analysis of THC-interacting proteins

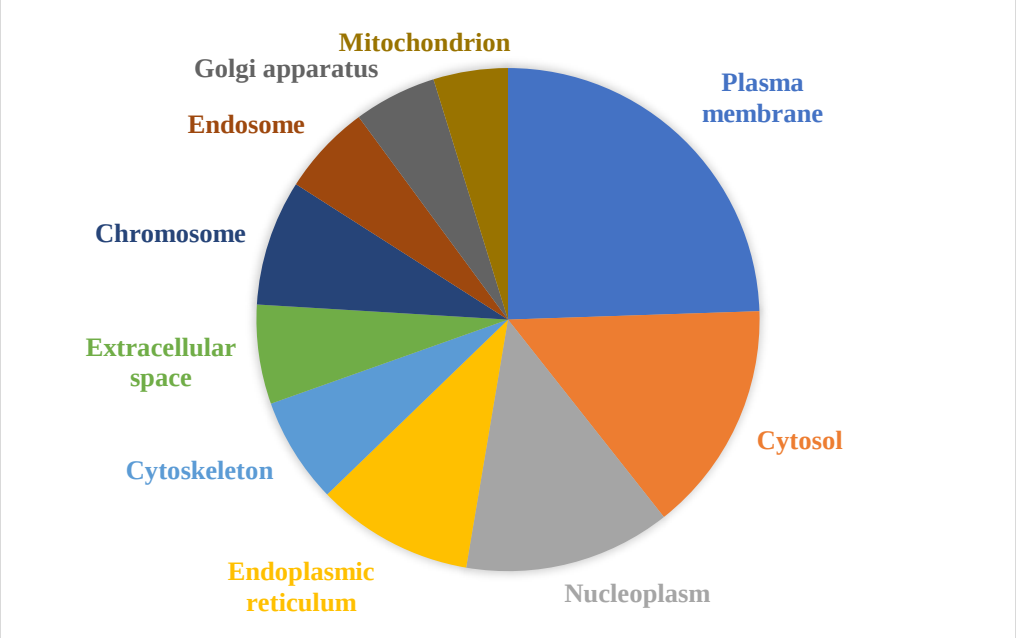
Functional analysis exhibited that THC-interacting proteins are associated with numerous human biological processes, including anatomical structure development, signaling, programmed cell death, and the nervous system (Figure 2A). Previous investigations have shown that THC can affect molecular activities such as oxidoreductase activity, molecular transducer activity, and transferase activity (Figure 2B). These proteins also interact with the cytosol, nucleoplasm, chromosomes, and plasma membrane (Figure 2C).



(A)



(B)



(C)

Figure 2. Functional annotation analysis of THC-interacted proteins showed the various biological processes (A), molecular functions (B), and localization of cellular components (C).

Identification of human proteins that interact with CBD

Ten crucial proteins that interact with cannabidiol (CBD) were found by PCI analysis: CNR1, TRPV2, CNR2, CYP2C19, CYP2C9, CYP2D6, CYP2B6, KRT10, CYP1A1, and CYP1A2. These proteins are connected with an additional 100 human proteins identified by PPIs from the STRING database (Figure 3).

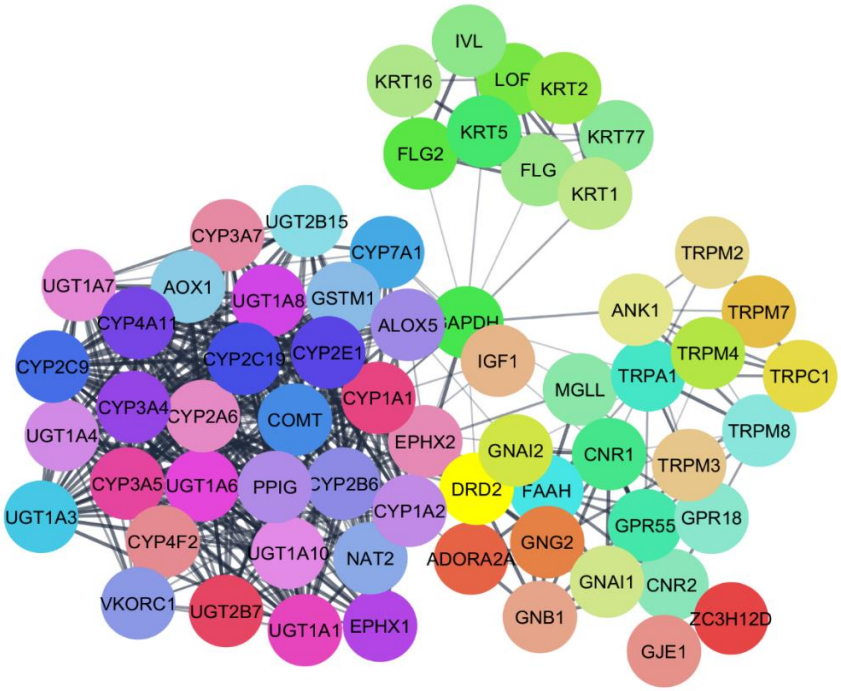
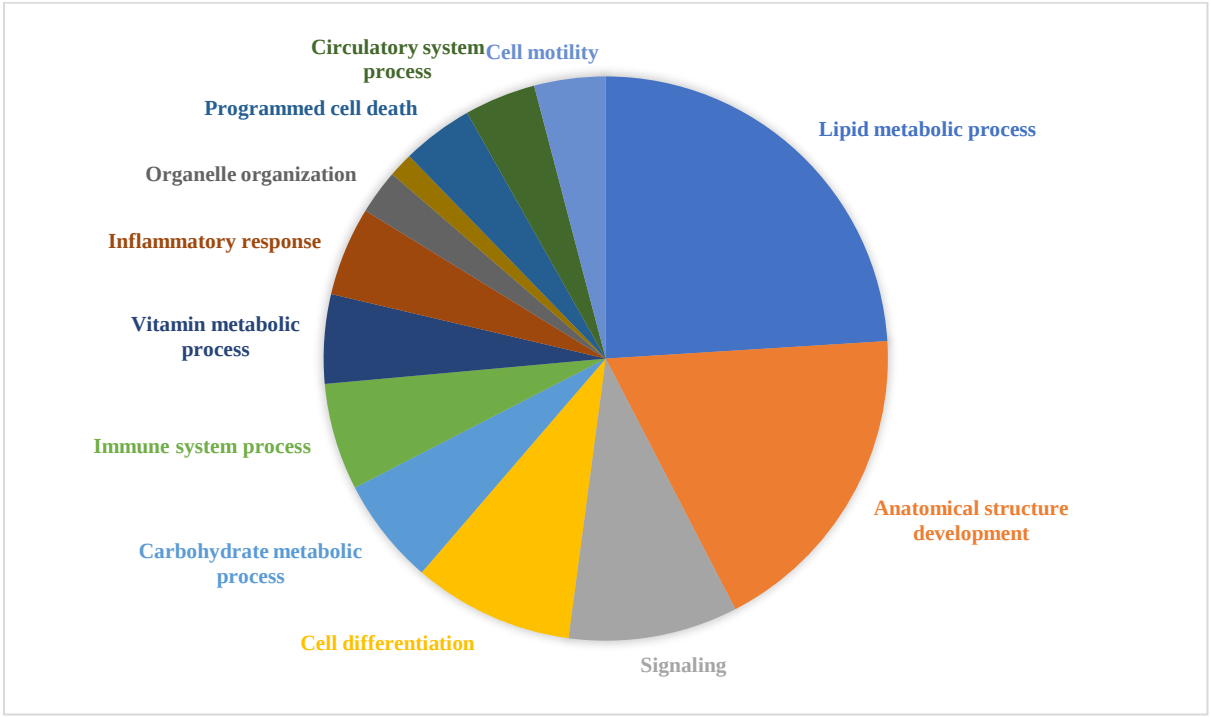


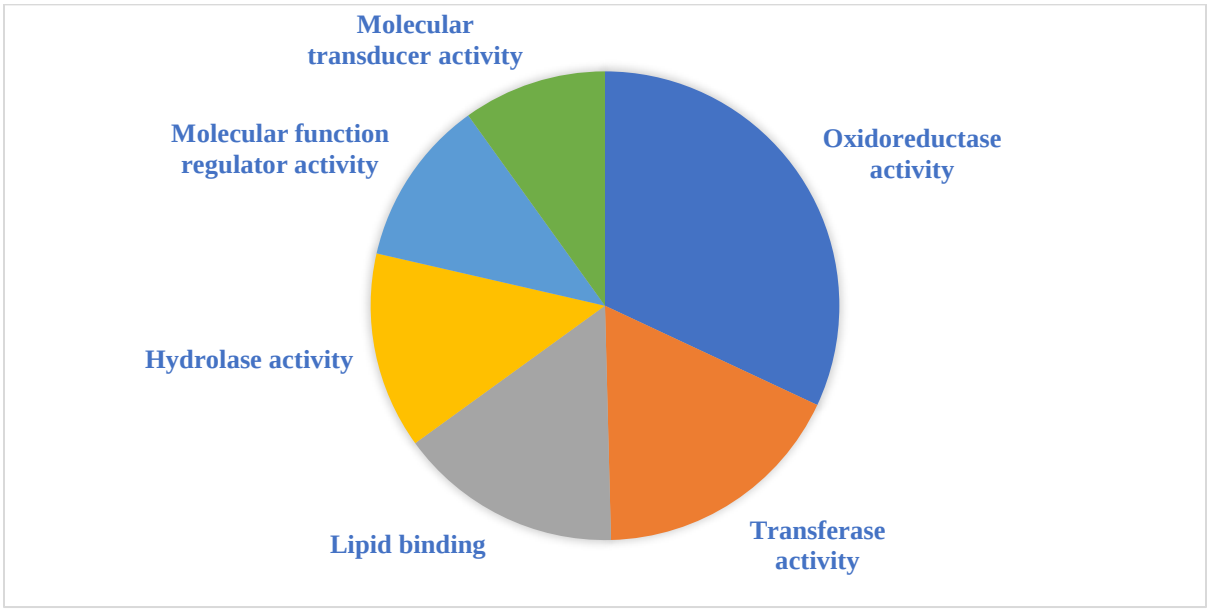
Figure 3. Protein-protein interaction (PPI) of CBD identified via STRING 12.0

Functional analysis of CBD-interacted proteins

Functional analysis exhibited that CBD-interacting proteins are associated with numerous human biological processes, molecular functions, and cellular components, including anatomical structure development, lipid metabolic process, carbohydrate metabolism, cell differentiation, oxidoreductase activity, molecular transducer activity, and transferase activity, cytosol, nucleoplasm, chromosomes, and plasma membrane (Figure 4).



(A)



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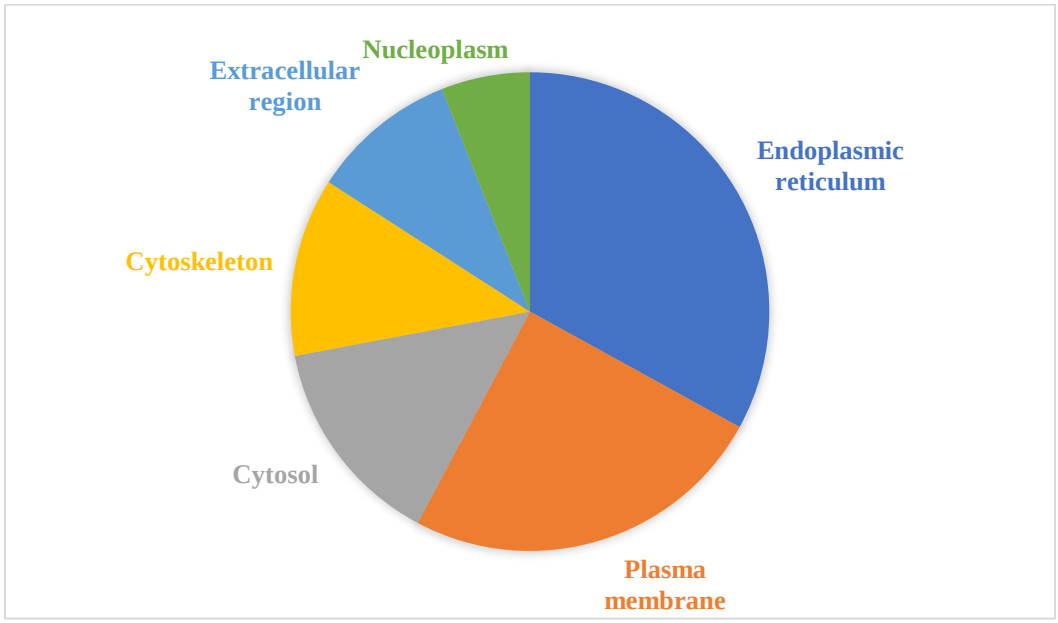
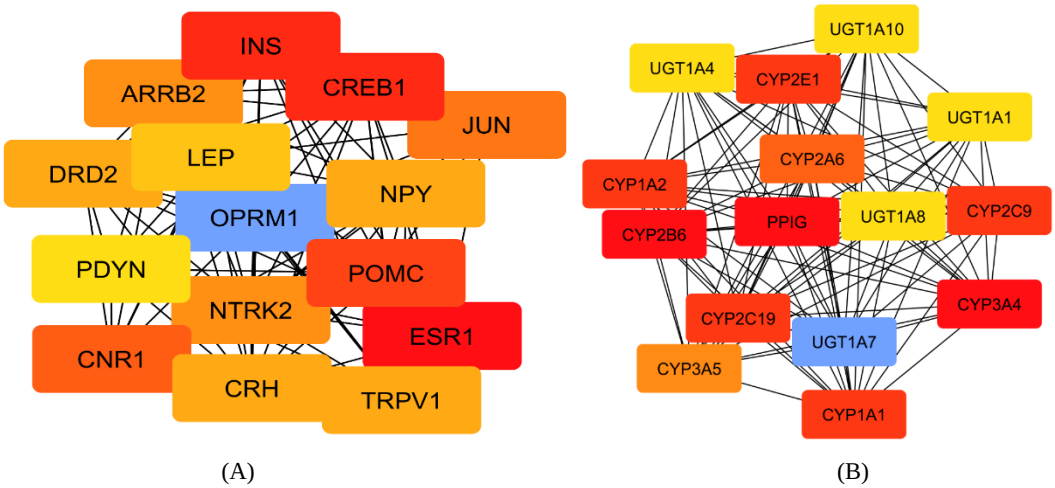


(C)

Figure 4. Functional annotation analysis of CBD-interacted proteins showed the various biological processes (A), molecular functions (B), and localization of cellular components (C).

Identification of crucial proteins that interact with THC and CBD

This study aimed to identify proteins interacting with delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) to predict their potential effects on the human body. Initially, 98 THC and 90-CBD-associated proteins were analyzed using Cytoscape to construct a STRING interaction network. The graphical representations of each protein's interaction networks are shown in Figure 5. Based on degree centrality, 15 THC-interacted proteins were identified that belong to the highest degree centrality: ESR1, CREB1, INS, POMC, CNR1, JUN, NTRK2, ARRB2, CRH, NPY, DRD2, TRPV1, OPRM1, LEP, and PDYN. Among these, ESR1 exhibited the highest centrality with a node degree of 48, while PDYN had the lowest with a node degree of 26 (Table 1). Similarly, 15 CBD-associated proteins were also identified, including CYP2B6, PPIG, CYP3A4, CYP1A2, CYP2E1, CYP2C9, CYP2C19, CYP1A1, CYP2A6, CYP3A5, UGT1A7, UGT1A10, UGT1A4, UGT1A1, and UGT1A8. The highest central node identified in this study is 31, which was found in three proteins: CYP2B6, PPIG, and CYP3A4. The lowest central node was found in UGT1A10, UGT1A4, UGT1A1, and UGT1A8, and the node was 26 (Table 1).



(A) (B)

Figure 5. Top 15 critical proteins based on degree centrality that interacted with THC (a) and CBD (b).

Table 1. Crucial proteins with degree centrality that interacted with THC and CBD.

THC			CBD		
Rank	**Protein**	**Degree centrality**	**Rank**	**Protein**	**Degree centrality**
1	ESR1	48	1	CYP2B6	31
2	CREB1	41	2	PPIG	31
3	INS	41	3	CYP3A4	31
4	POMC	38	4	CYP1A2	30
5	CNR1	33	5	CYP2E1	30
6	JUN	32	6	CYP2C9	30
7	NTRK2	29	7	CYP2C19	30
8	ARRB2	29	8	CYP1A1	30
9	CRH	28	9	CYP2A6	29
10	NPY	2 8	10	CYP3A5	28
11	DRD2	28	11	UGT1A7	27
12	TRPV1	28	12	UGT1A10	26
13	OPRM1	27	13	UGT1A4	26
14	LEP	27	14	UGT1A1	26
15	PDYN	26	15	UGT1A8	26

Critical pathways that are regulated by identified crucial proteins

The analysis of the clustergram for ESR1, CREB1, INS, POMC, CNR1, JUN, and NTRK2 indicated their association with several Reactome pathways, including PIP3 activates AKT signaling, intracellular signaling by second messengers, and diseases of signal transduction by growth factor receptors and second messengers, among others, as shown in Table 2. Alternately, the KEGG clustergram showed that these crucial proteins predominantly influence the PIP3 activation of AKT signaling, intracellular signaling by second messengers, diseases of signal transduction by growth factor receptors, and second messengers, among others, as shown in Table 2. The p-value analysis indicates a significant interaction between these proteins and THC. The p-value analysis indicates a significant interaction between these proteins and THC.

Table 2. Reactome and KEGG clustering pathways of ESR1, CREB1, INS, POMC, CNR1, JUN, and NTRK2 that interacted with THC.

Index	Reactome pathway	P-value	Respected proteins
1	Signal Transduction	6.452e-7	CYP2C9, CYP2B6, CYP1A2, CYP1A1, CYP2E1, CYP3A4, CYP2C19
2	PIP3 Activates AKT Signaling	0.000001291	CYP2C9, CYP2B6, CYP1A2, CYP1A1, CYP2E1, CYP3A4, CYP2C19
3	Intracellular Signaling by Second Messengers	0.000002194	CYP2C9, CYP2B6, CYP1A2, CYP1A1, CYP2E1, CYP3A4, CYP2C19
4	Diseases of Signal Transduction by Growth Factor Receptors and Second Messengers	0.000008462	CYP2C9, CYP1A2, CYP1A1, CYP2E1, CYP3A4
5	Generic Transcription Pathway	0.00001651	CYP2C9, CYP1A2, CYP1A1, CYP2E1, CYP3A4
6	RNA Polymerase II Transcription	0.00002700	CYP2C9, CYP2B6, CYP1A2, CYP1A1, CYP2E1, CYP3A4, CYP2C19
7	ESR-mediated Signaling	0.00002963	CYP2C9, CYP1A2, CYP2E1, CYP3A4
8	GPCR Downstream Signalling	0.00003224	CYP2C9, CYP1A2, CYP1A1, CYP2C19
9	Signaling by NOTCH	0.00003817	CYP2C9, CYP1A2, CYP2E1, CYP3A4
10	FOXO-mediated Transcription of Oxidative Stress, Metabolic and Neuronal Genes	0.00004859	CYP2C9, CYP1A2, CYP1A1, CYP2C19
	KEGG pathway		
1	Estrogen signaling pathway	7.257e-8	CYP2C9, CYP2B6, CYP1A2, CYP1A1, CYP2E1, CYP3A4,
2	Chemical carcinogenesis	6.767e-7	CYP2C9, CYP1A2, CYP2E1, CYP3A4, CYP2C19

3	Relaxin signaling pathway	0.000009003	CYP2C9, CYP2B6, CYP1A2, CYP1A1, CYP2E1, CYP3A4, CYP2C19
4	cAMP signaling pathway	0.00004211	CYP2C9, CYP2B6, CYP1A2, CYP2E1, CYP3A4, CYP2C19
5	MAPK signaling pathway	0.0001053	CYP2C9, CYP2B6, CYP1A2, CYP1A1, CYP3A4
6	Cocaine addiction	0.0001225	CYP1A2, CYP1A1, CYP2E1, CYP3A4,
7	Cortisol synthesis and secretion	0.0002161	CYP2C9, CYP2B6, CYP2E1, CYP2C19
8	Amphetamine addiction	0.0002436	CYP2C9, CYP2B6, CYP1A1
9	Prolactin signaling pathway	0.0002507	CYP1A2, CYP1A1
10	Insulin secretion	0.0003784	CYP2C9, CYP2C19

Alternately, the clustergram analysis of CYP2B6, PPIG, CYP3A4, CYP1A2, CYP2E1, CYP2C9, and CYP2C19 found that these are associated with numerous Reactome pathways, including Xenobiotics, Phase I-Functionalization of Compounds, Biosynthesis of DHA-derived SPMs, Biological Oxidations, and others shown in Table 3. Alternately, these proteins also strongly interacted with various KEGG pathways, including Metabolism of xenobiotics by cytochrome P450, Drug metabolism, Steroid hormone biosynthesis, and others (Table 3).

Table 3. Reactome and KEGG clustering pathways of CYP2B6, PPIG, CYP3A4, CYP1A2, CYP2E1, CYP2C9, and CYP2C19 that interacted with CBD.

Index	**Reactome pathway**	**P-value**	**Respected proteins**
1	Xenobiotics	1.089e-20	CYP2C9, CYP2B6, CYP1A2, CYP1A1, CYP2E1, CYP3A4, CYP2C19
2	Cytochrome P450 - Arranged by Substrate Type	2.188e-17	CYP2C9, CYP2B6, CYP1A2, CYP1A1, CYP2E1, CYP3A4, CYP2C19
3	Phase I - Functionalization of Compounds	7.142e-16	CYP2C9, CYP2B6, CYP1A2, CYP1A1, CYP2E1, CYP3A4, CYP2C19
4	Biosynthesis of DHA-derived SPMs	1.298e-14	CYP2C9, CYP1A2, CYP1A1, CYP2E1, CYP3A4

5	Biosynthesis of Specialized Proresolving Mediators (SPMs)	2.438e-14	CYP2C9, CYP1A2, CYP1A1, CYP2E1, CYP3A4
6	Biological Oxidations	1.496e-13	CYP2C9, CYP2B6, CYP1A2, CYP1A1, CYP2E1, CYP3A4, CYP2C19
7	Biosynthesis of Maresin-Like SPMs	1.574e-13	CYP2C9, CYP1A2, CYP2E1, CYP3A4
8	Synthesis of Epoxy (EET) and Dihydroxyeicosatrienoic Acids (DHET)	7.345e-13	CYP2C9, CYP1A2, CYP1A1, CYP2C19
9	Biosynthesis of Maresins	7.345e-13	CYP2C9, CYP1A2, CYP2E1, CYP3A4
10	Synthesis of (16-20)-Hydroxyeicosatetraenoic Acids (HETE)	1.322e-12	CYP2C9, CYP1A2, CYP1A1, CYP2C19
KEGG pathways			
1	Metabolism of xenobiotics by cytochrome P450	6.847e-14	CYP2C9, CYP2B6, CYP1A2, CYP1A1, CYP2E1, CYP3A4,
2	Linoleic acid metabolism	2.487e-13	CYP2C9, CYP1A2, CYP2E1, CYP3A4, CYP2C19
3	Chemical carcinogenesis	2.524e-13	CYP2C9, CYP2B6, CYP1A2, CYP1A1, CYP2E1, CYP3A4, CYP2C19
4	Drug metabolism	5.977e-13	CYP2C9, CYP2B6, CYP1A2, CYP2E1, CYP3A4, CYP2C19
5	Retinol metabolism	2.172e-11	CYP2C9, CYP2B6, CYP1A2, CYP1A1, CYP3A4
6	Steroid hormone biosynthesis	5.430e-9	CYP1A2, CYP1A1, CYP2E1, CYP3A4,
7	Arachidonic acid metabolism	5.430e-9	CYP2C9, CYP2B6, CYP2E1, CYP2C19
8	Lipid and atherosclerosis	0.00006593	CYP2C9, CYP2B6, CYP1A1
9	Tryptophan metabolism	0.0001196	CYP1A2, CYP1A1
10	Serotonergic synapse	0.0008665	CYP2C9, CYP2C19

Hypothetical direct interactions between THC and CBD with proteins obtained from STITCH

Collection and preparation of protein structures and ligands

The protein structures (PDBs) of CNR1, CNR2, CASP3, FOS, PDYN, GPR55, BDNF, POMC, CYP1B1, and PRL that interacted with THC and those of CNR1, TRPV2, CNR2, CYP2C19, CYP2C9, CYP2D6, CYP2B6, KRT10, CYP1A1, and CYP1A2 for CBD were obtained from the AlphaFold Protein Structure Database, and then prepared and visualized by MGL tools (AutoDock visualizer) v.1.5.7.

SwissADME results for THC and CBD medicinal compounds

The SwissADME calculated the characteristics of two ligands (chemicals): 29.46 Å2 TPSA (Topological Polar Surface Area) for THC and 40.46 Å2 for CBD; they have 4 and 6 rotatable bonds, respectively, and have no lead-like similarities with high GI absorption (Table 4). The results of Lipinski's Rule of 5 for the THC and CBD ligands are demonstrated in Table 5.

Table 4. Characteristics of ligands calculated with SwissADME.

Drug/Ligand	TPSA (Å²)	No. rotatable bond	Consensus LogP	GI Absorption	Water Solubility	Lead Likeness
Dronabinol/Delta 9-tetrahydrocannabinol (THC)	29.46	4	5.33	High	Moderately soluble	No
Cannabidiol	40.46	6	5.2	High	Moderately soluble	No

Table 5. Results of Lipinski's Rule of 5 for the THC and CBD ligands.

Drug/Ligand	Mass g/mol	H Acceptor	H Donor	Log P	Molar Refractivity
Delta9-tetrahydrocannabinol (THC)	314.5	4	1	5.7358	97.909
Cannabidiol	314.46	4	2	5.8465	99.849

Results of protein-ligand interactions

PyRx was utilized to dock the two ligands (THC and CBD) with the 20 selected proteins. The docking results (binding energy/affinity) for both THC and CBD have been showcased in Tables 6 and 7, respectively. Among the proteins binding with THC and CBD, those with the best binding affinity were -8.5 kcal/mol and -8 kcal/mol, respectively.

Table 6. PyRx Docking Results- mode and binding affinity for weed chemical THC found from STITCH.

Protein-Ligand	Mode	Binding Affinity
Cannabinoid receptor 1	1	-6.3
	2	-5.9
Cannabinoid receptor 2	1	-6.1
	2	-6
Caspase-3	1	-6.6
	2	-6
Protein c-Fos	1	-6.8
	2	-6.7
Pre-prodynorphin	1	-8.5
	2	-8.2
G-protein coupled receptor 55	1	-6.8
	2	-6.7
Brain-derived neurotrophic factor	1	-6.5

	2	-6.3
Pro-opiomelanocortin	1	-5.9
	2	-5.8
Cytochrome P450 1B1	1	-7.6
	2	-7
Prolactin	1	-6.7
	2	-6.7

Table 7. PyRx Docking Results- mode and binding affinity for weed chemical CBD found from STITCH.

Protein-Ligand	Mode	Binding Affinity
Cannabinoid receptor 1	1	-6.9
	2	-6.7
Transient receptor potential cation channel subfamily V member 2	1	-6.2
	2	-6.1
Cannabinoid receptor 2	1	-7.4
	2	-7.1
Cytochrome P450 2C19	1	-6.6
	2	-6.3
Cytochrome P450 2C9	1	-6.8
	2	-6.5
Cytochrome P450 2D6	1	-7.7
	2	-7.4
Cytochrome P450 2B6	1	-6.3
	2	-6.2
Keratin, type I cytoskeletal 10	1	-7.6
	2	-7.4
Cytochrome P450 1A1	1	-8
	2	-7.7
Cytochrome P450 1A2	1	-6.9
	2	-6.8

THC predominantly interacted with tyrosine, phenylalanine, and aspartate with Alkyl, Pi-Alkyl, Pi-Pi and Unfavorable acceptor-acceptor bonds, and CBD interreacted with valine, leucine, glycine, phenylalanine, alanine, isoleucine, and cysteine with Pi-sigma, Pi-alkyl, Amide-Pi and Alkyl bonds. The docking results are illustrated in Figures 6 and 7 for THC and in Figures 8 and 9 for CBD. The binding affinities indicate that the proteins are perfect for robust docking.

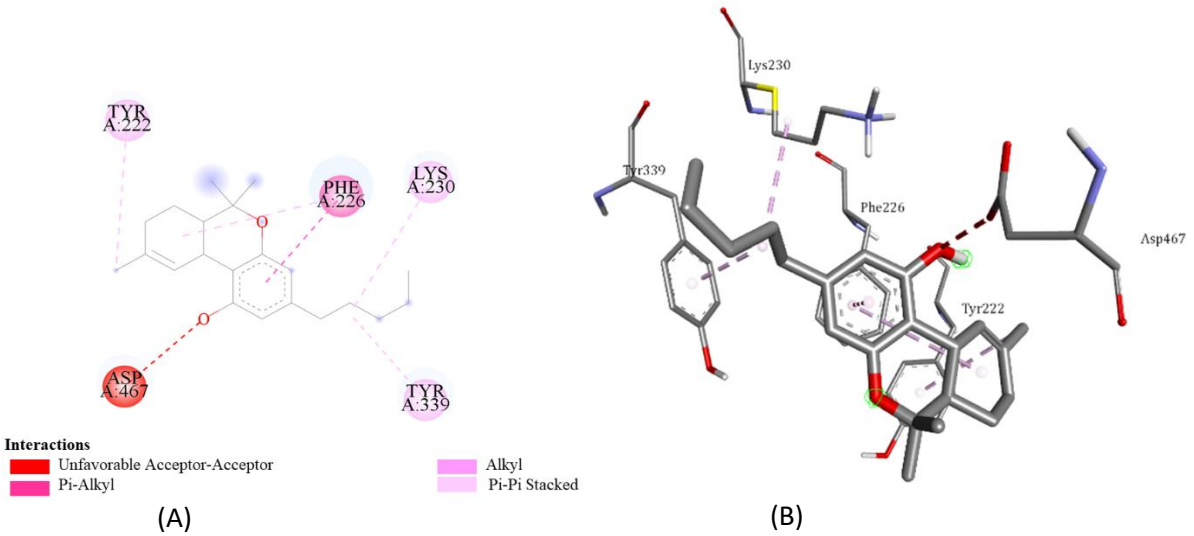


Figure 6. (A) 2D interaction of THC with target protein Preprodynorphin, (B) 3D interaction of THC with target protein Preprodynorphin visualized by Biovia Discovery Studio.

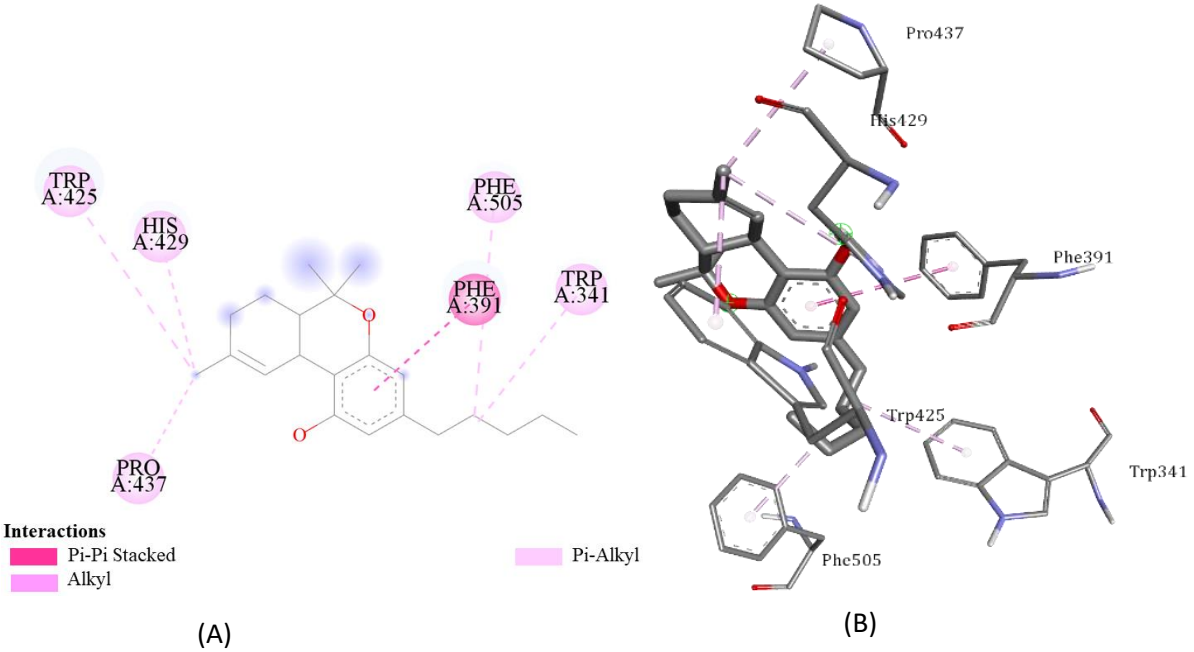


Figure 7. (A) 2D interaction of THC with target protein Cytochrome P450 1 B1, (B) 3D interaction of THC with target protein Cytochrome P450 1 B1 visualized by Biovia Discovery Studio.

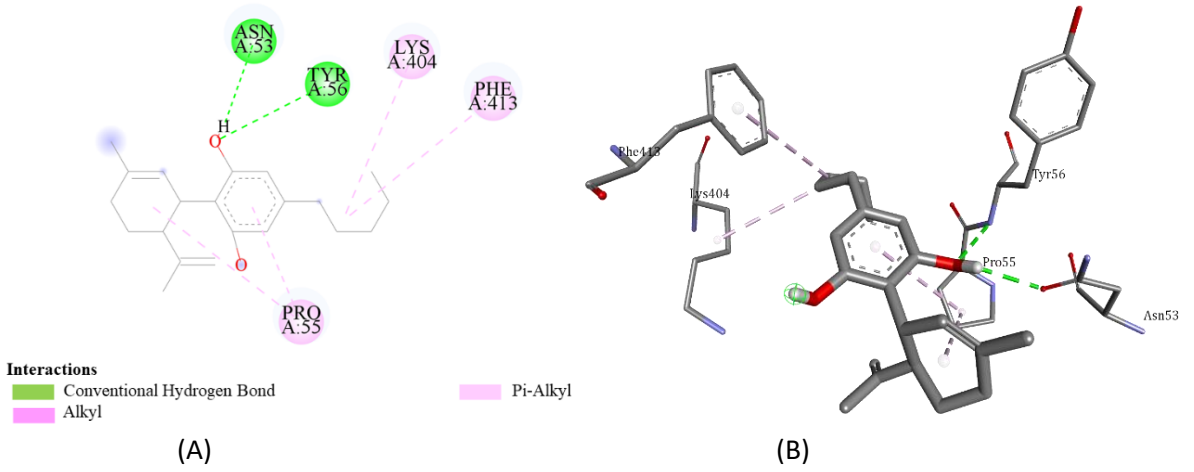


Figure 8. (A) 2D interaction of CBD with target protein Cytochrome P450 2D6, (B) 3D interaction of CBD with target protein Cytochrome P450 2D6 visualized by Biovia Discovery Studio.

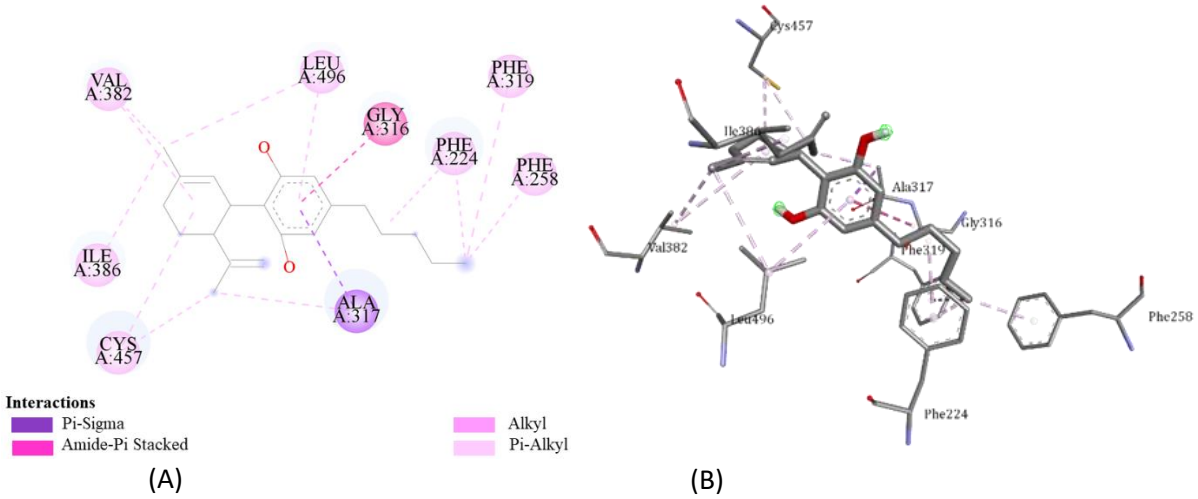


Figure 9. (A) 2D interaction of CBD with target protein Cytochrome P450 1A1, (B) 3D interaction of CBD with target protein Cytochrome P450 1A1 visualized by Biovia Discovery Studio.

Discussion

Cannabis is the most widely cultivated, trafficked, and abused illicit drug in the world. Several studies suggest the beneficial and detrimental impacts of two bioactive compounds of cannabis, delta 9-tetrahydrocannabinol (THC) and cannabidiol (CBD), on human health (Datta *et al.*, 2021; Preteroti *et al.*, 2023). Both THC and CBD become available in the bloodstream via the lungs when cannabis is smoked and impact the human body by interacting with several proteins that modulate many metabolic and signaling pathways (Podinić and Raha, 2023). This bioinformatics study contributes to finding out the possible number of proteins and their functions, functional annotation and pathway analysis of these proteins, and possible interacted genes related to several diseases (e.g., metabolic diseases, immune diseases, nerve diseases, and different types of cancers), and some medicines that are produced from weed products that can be used to treat several human disorders.

THC and CBD were found to interact with 166 functional proteins related to human health. Similarly, rutin is a flavonoid found in plants, including cannabis, that interacts with 100 and quercetin interacts with 99 human proteins; both of them help to reduce oxidative stress (Osman *et al.*, 2023). These compounds perform agonist effects at the prototypical cannabinoid receptors, CB1 and CB2, located on neurons and immune cells that respond to immunological or anti-inflammatory potential (Boggs *et al.*, 2018). Also, weed smoking regulates the cellular functions of the respiratory tracts, impaired immune and pulmonary function, and neoplastic effects (Owen *et al.*, 2014). Moreover, Rong *et al.* (2018) demonstrated that the hepatic biotransformation of psychotropic agents involves cytochrome P_{450} enzymatic pathways, which THC and CBD can inhibit. Furthermore, the use of weed clinically helps prevent potential drug-drug interactions in patients receiving specific psychotropic agents. Equally, new studies have shown that cannabis compounds have some therapeutic benefits for treating a variety of illnesses, like pain in adults and mental and neurological diseases (Abrams, 2018).

THC and CBD regulate several biological processes and signaling pathways of the human body. These phytochemicals modulate cell signaling, cell differentiation, anatomical structure development, programmed cell death, inflammatory response, carbohydrate and lipid metabolism, nerve control, etc. Furthermore, these bioactive compounds directly correlate with the cell's subcellular organelles. They were found to interact with cell membranes, nucleoplasm, endoplasmic reticulum, cytoskeleton, and extracellular space. Moreover, THC was found to be involved with mitochondria, cytosol, chromosomes, nucleosomes, and cytoskeleton alone. CBD can facilitate some signaling events of cells, such as cellular differentiation, cell death, and homeostasis, through mitochondrial structural and functional modification (Podinić and Raha, 2023). Furthermore, (James *et al.*, 2022) found that THC and CBD adversely affect cell membrane integrity and increase the viscosity of red blood cells. According to Walker *et al.* (2020) THC at a low concentration (20 µM) may impair mitochondrial function, but the integrity of the plasma membrane remains unchanged.

Similarly, we found a direct correlation between CBD and chromosomes, and previous studies suggest that chromosomal aberrations and DNA damage may result from CBD interactions, even at low concentrations (Reece and Hulse, 2016; Russo *et al.*, 2019). Moreover, THC can impair brain function through histone modification of nucleosomes, where nucleosomal positioning and gene transcription are necessarily disrupted (Reece and Hulse, 2023). The *in-silico* approach also retrieved molecular functions of different proteins where THC and CBD are commonly found to regulate hydrolase activity, transferase activity, and lipid binding activity in the human body. Additionally, catalytic activity, DNA binding, and receptor-ligand activity were also included by THC alone.

Identifying the critical nodes in a network by centrality degree analysis facilitates the examination of its topology, encompassing its strength and susceptibility to attacks. Degree

centrality, interaction centrality, and proximity centrality are employed to evaluate social influence within networks (Sheikh *et al.*, 2025). Based on degree centrality, THC interacts strongly with the estrogen receptor 1 (ESR1) gene, which regulates numerous biological functions, particularly in reproductive organs, breast tissue, and the blood vessels (Nilsson and Gustafsson, 2002). By changing immunological responses, THC can downregulate ESR1 expression and affect cell proliferation, differentiation, and hormone balance, therefore promoting tumor growth (Moreno *et al.*, 2020). Additionally, THC exhibits considerable binding affinity for cyclic AMP response element-binding protein 1 (CREB1) and the insulin (INS) gene, both of which are crucial to neural development, memory, learning, and insulin resistance (Scott Bitner, 2012). THC negatively influences the activation of both the CREB1 and INS genes; (Lundqvist, 2005) stated that excessive cannabis consumption leads to cognitive memory loss and low insulin production. Alternately, CBD strongly interacted with cytochrome P450 family 2 subfamily B member 6 (CYP2B6), peptidylprolyl isomerase G (PPIG), and cytochrome P450 family 3 subfamily A member 4 gene; these genes are responsible for the metabolism of xenobiotics by liver enzymes, cell cycle control, nuclear signaling, and metabolism of toxins and drugs respectively. Chronic weed smoking causes different metabolic disorders, including visceral adiposity, hepatic steatosis, and hampered toxin metabolism (Muniyappa *et al.*, 2013).

Hypothetical molecular interactions demonstrated that THC had a strong interaction with pre-prodynorphin protein, characterized by a binding energy of -8.5 kcal/mol, which is essential in the neurological system, especially in regulating pain and emotional reactions (Koneru *et al.*, 2009). Acute THC exposure raises PDYN gene expression in some brain areas, which produces more dynorphin peptides activating kappa-opioid receptors (KORs). This can cause dysphoria or anxiety by lowering dopamine release (Hasbi *et al.*, 2023). Chronic THC exposure downregulates PDYN expression, perhaps leading to tolerance, modifications in emotional modulation, and altered stress responses (Machado *et al.*, 2024). Similarly, THC interacts with the Cytochrome P450 1B1 protein, exhibiting a binding energy of -7.6 kcal/mol, which plays a crucial role in the metabolism of various toxins, drugs, and xenobiotics (Anzenbacher and Anzenbacherová, 2001). Prolonged exposure to THC has detrimental effects on the metabolism of these substances by altering this protein (Sharma *et al.*, 2012). Conversely, CBD had a robust interaction with the Cytochrome P450 1A1 protein, demonstrating a binding energy of -8 kcal/mol; this enzyme is crucial to the metabolism of hazardous substances. In contrast, CBD upregulates this protein, leading to carcinogenesis and metabolic instability (Court *et al.*, 2024). Cytochrome P450 family 2 subfamily D member 6 is responsible for the metabolism of ingested drugs, and chronic CBD levels adversely affect its functions (metabolism of antidepressants, opioids, beta blockers, and antipsychotics) (Balachandran *et al.*, 2021).

Cannabis and its derivatives are widely utilized to treat a variety of human illnesses. Moreover, Legare *et al.* (2022) demonstrated that CBD oils are used for therapeutic purposes that relieve pain, seizures, and sleep disorders, and cannabidiol helps to treat CNS disorders and brain tumors like Glioblastoma, as well as inhibiting human breast cancer cell proliferation (Ivanov *et al.*, 2017; McAllister *et al.*, 2011; Scuderi *et al.*, 2009). But chronic use of cannabis causes cell death or survival involved in cancer, stimulated by autophagy. Salazar *et al.* (2009) demonstrated that THC is responsible for human glioma cell death via promoting autophagy. Our study merely investigated the potential impacts of THC and CBD; further, we need animal studies to show the positive and negative effects of these chemicals on human health.

Conclusion

Our study identified some proteins that interact with THC and CBD, and the possible functions (biological, molecular, and cellular) of these proteins are directly or indirectly affected by these compounds. These bioinformatics approaches have visibly discovered some cancer-causing and life-threatening genes such as CNR1, CNR2, Caspase-3, FOS, GPR55, BDNF, and TRPV2; GPR55 is responsible for colorectal cancer, CNR2 induces blood cancer, and CNR1 increases type 2 diabetes mellitus, so these genes bring some life-threatening diseases to the human body. THC and CBD adversely influence estrogen functions (breast tissue development and female reproductive system maintenance), memory development, memory loss, depression, insulin activity, xenobiotics, and drug metabolism through their interaction with their responsive proteins. Significantly, these compounds are used to treat a variety of fatal conditions. Alcoholism and morphine addiction are induced considerably by cannabidiol, and the FOS gene is responsible for cocaine addiction. It has been proven that extreme utilization of weed causes different well-being issues and potential impacts on adult human health. The limitation of this study is that it needs to declare the typical roles of these proteins here, and additional *in vitro and in vivo* studies are required to illustrate the rest. Therefore, authorities should raise awareness and take essential steps to reduce weed smoking among adults and younger people.

Authors Contributions

Md. Ramjan Sheikh: Conceptualization, Methodology, Formal analysis, Writing original draft. Shyam Sundar Shaha: Investigation, Writing, review and editing. Akhi Akter: Methodology, writing original draft. Ruku Akter: Methodology, writing original draft. Mehadi Hasan Evan: Writing, review and editing. Mst. Tasmina Akter: Methodology. Md. Rifat Ahmed: Methodology. Jwel Sharma: Methodology, writing original draft. Mita Rani Das: Methodology. Yousuf Al Mamun: Data curation. Md. Abdullah: Writing, review and editing. Md. Liton Miah: Data curation. Elachi Akter: Investigation.

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Conflict of interest statement

The authors declare no conflicts of interest.

Data availability

All research data are provided in the current article.

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