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Exploring the Therapeutic Potential of Cannabis Constituents in Parkinson's Disease: Insights from Molecular Docking Simulations

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Abstract: *Cannabis sativa* L., an herbaceous plant from the Cannabaceae family, contains numerous phytochemicals with potential neuroprotective properties. Among the neurodegenerative disorders, Parkinson's disease (PD) has emerged as a major global health concern. In the present study, a comprehensive *in silico* analysis was conducted to evaluate the interaction between cannabis-derived compounds and monoamine oxidase B (MAO-B), a key enzyme implicated in the progression of PD. Molecular docking revealed that Cannabicyclol, a phytochemical from *Cannabis sativa*, exhibited a strong binding affinity with MAO-B, achieving a docking score of −10.8 kcal/mol. Further analysis of physicochemical properties, drug-likeness, toxicity, and ADMET profiles supported the therapeutic potential of Cannabicyclol. Molecular dynamics simulations conducted over 100 ns confirmed the structural stability of the MAO-B–Cannabicyclol complex and demonstrated stable protein–ligand interactions throughout the simulation period. In addition, trajectory analyses, including root mean square deviation and root mean square fluctuation evaluations, indicated minimal conformational fluctuations within the binding pocket of the protein. These *in silico* findings suggest that Cannabicyclol has the potential to act as an MAO-B inhibitor and warrants further experimental validation as a candidate for PD treatment.

Keywords: *Cannabis sativa* L., Parkinson's disease, MAO-B, molecular docking, molecular dynamics simulations

1. Introduction

Cannabis sativa L., commonly known as cannabis, has long been used in traditional medicines worldwide for centuries to alleviate a variety of ailments [1]. The plant's medicinal and recreational applications are primarily determined by the presence of specific compounds known as cannabinoids. The recent surge in cannabis-related research, clinical trials, and regulatory shifts reflects a profound global transformation in attitudes toward its use. Notably, the FDA's approval of *Epidiolex*®, the first cannabis-derived drug for the treatment of severe seizure disorders, signifies a groundbreaking step in the integration of cannabis into mainstream medical practice. Furthermore, the global market for cannabidiol (CBD) products is expected to reach an astounding $1.9 billion by 2020 [2].

Over 565 distinct constituents have been identified in *Cannabis sativa* [3], with more than 150 of these compounds classified as phytocannabinoids [4–6]. The Δ9-tetrahydrocannabinol (THC) is the main psychoactive component of *Cannabis*, while Cannabidiol (CBD), the main non-psychoactive component, has recently emerged as a potential prototype for drug development due to its antioxidant and anti-inflammatory properties coupled with its favorable pharmacological profile and excellent tolerability [7]. Beyond these, cannabis contains additional cannabinoids categorized into seven distinct classes, including Cannabinol (CBN), Cannabinodiol (CBND), Cannabitriol (CBT), Cannabielsoin (CBE), Cannabichromene (CBC), Cannabicyclol (CBL), and other miscellaneous types [8]. These cannabinoids exert a wide range of biological effects by interacting with various receptors, primarily the CB1 and CB2 cannabinoid receptors, as well as other non-cannabinoid receptors such as G-protein-coupled receptors (GPCRs) (GPR55, GPR3) and ion channels [9]. The therapeutic potential of cannabis extends to a variety of conditions, suggesting its promise as an alternative treatment for diseases such as chronic pain, multiple sclerosis, schizophrenia, glaucoma, inflammatory bowel diseases, epilepsy, anxiety, Alzheimer's disease, Parkinson's disease (PD), Huntington's disease, and even COVID-19 [10].

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Notably, phytocannabinoids can bind to specific GPCRs, as summarized in Table 1, highlighting their vast potential in medical applications [11].

PD is a progressive neurodegenerative disorder marked by the degeneration of dopaminergic neurons in the substantia nigra [22]. The loss of dopamine-producing neurons results in the characteristic motor symptoms of PD, such as tremors, rigidity, and bradykinesia [23]. The disease's pathophysiology is complex, and while much of the focus has been on dopamine replacement therapy, researchers have increasingly turned their attention to the molecular mechanisms that underlie neurodegeneration [24]. Among the most significant contributors are alpha-synuclein, monoamine oxidase B (MAO-B), and the A2A adenosine receptor, each playing crucial roles in disease progression. Among the key contributors to PD, MAO-B plays a pivotal role in disease progression by catalyzing the oxidative deamination of dopamine, leading to increased oxidative stress and neuronal damage. [25].

MAO-B is an enzyme responsible for the breakdown of dopamine in the brain. In PD, the activity of MAO-B is upregulated, accelerating the degradation of dopamine and worsening disease symptoms [25]. As dopamine levels decline, patients experience a decrease in motor function and cognitive abilities. Inhibiting MAO-B activity with drugs like *selegiline* and *rasagiline* has proven effective in managing symptoms by preserving dopamine levels and offering neuroprotective effects [26]. Newer MAO-B inhibitors such as *safinamide* also have additional benefits by modulating glutamate release, offering further symptomatic relief [27].

While existing inhibitors targeting alpha-synuclein aggregation, MAO-B activity, and A2A receptor signaling offer promising therapeutic benefits for PD, they are associated with various side effects [28]. MAO-B inhibitors like *selegiline* and *rasagiline* can cause nausea, insomnia, and serotonin syndrome when combined with certain medications, while *istradefylline*, an A2A receptor antagonist, may lead to dyskinesia and hallucinations [29, 30]. To address these issues, cannabis plant-derived compounds have emerged as potential alternatives, offering neuroprotective effects with fewer side effects in recent days. These natural compounds, such as cannabidiol (CBD) and tetrahydrocannabinol (THC), exhibit anti-inflammatory, antioxidant, and neuroprotective properties and may provide safer, multi-targeted approaches for inhibiting key proteins involved in PD. Cannabis compounds have shown promise in modulating neurodegenerative pathways, potentially reducing the need for synthetic drugs and minimizing adverse effects, making them a promising option for improving the management of PD (Figure 1) [31].

Given the multifactorial nature of PD, multi-target therapeutic approaches are increasingly favored. This study aimed to perform comprehensive molecular docking analyses, complemented by molecular dynamics (MD) simulations, to evaluate the therapeutic potential of selected *Cannabis sativa* constituents. The study further examined physicochemical properties,

Table 1. Primary metabolites reported in *Cannabis sativa* and their therapeutic properties

Cannabinoid	Medical uses	Notes
Cannabidiol	Epilepsy (Dravet and Lennox–Gastaut syndromes), chronic pain, anxiety, insomnia, neuroprotection, neurodegenerative diseases (e.g., Alzheimer's, Parkinson's)	FDA-approved as Epidiolex for epilepsy; well-studied for anti-inflammatory and neuroprotective properties, especially in neurodegenerative diseases [12]
Tetrahydrocannabinol	Pain relief, nausea/vomiting (chemotherapy), appetite stimulation, sleep disorders, neurodegenerative diseases	Psychoactive; used in FDA-approved drugs like dronabinol and nabilone, may provide neuroprotection in diseases like Alzheimer's and Parkinson's [13, 14]
Cannabicyclol	Potential anti-inflammatory, neuroprotective, and antimicrobial effects; may aid sleep	Research is in early stages; may modulate serotonin receptors and help in neurodegenerative conditions [15, 16]
Cannabidivarin	Seizure disorders, autism spectrum disorder (ASD), potential gastrointestinal applications	Clinical trials are underway for ASD and neurodegenerative diseases like Prader–Willi syndrome [17]
Tetrahydrocannabivarin	Appetite suppression, weight loss, metabolic disorders, neuroprotection, neurodegenerative diseases	May improve insulin sensitivity, reduce appetite, and offer neuroprotective benefits in neurodegenerative diseases [18]
Cannabinol	Sleep disorders, neuroprotection, potential appetite stimulation, neurodegenerative diseases	May improve sleep quality and reduce nighttime awakenings; potential neuroprotective effects [19]
Cannabichromene	Anti-inflammatory, analgesic, antidepressant, antimicrobial, neuroprotective, potential neurodegenerative disease therapy	Shows promise in treating conditions like arthritis, inflammatory bowel diseases, and neurodegenerative diseases [16]
Cannabigerol	Anxiety, depression, neurodegenerative diseases (e.g., Alzheimer's, Parkinson's), pain, inflammation, cancer	Demonstrated anxiolytic and antidepressant effects; may inhibit cancer cell proliferation and protect against neurodegeneration [20]
Cannabigerolic acid	Precursor to CBG; potential anti-inflammatory, neuroprotective effects, may help in neurodegenerative diseases	Limited direct research; CBGA is the acidic precursor to CBG with potential neuroprotective properties [21]

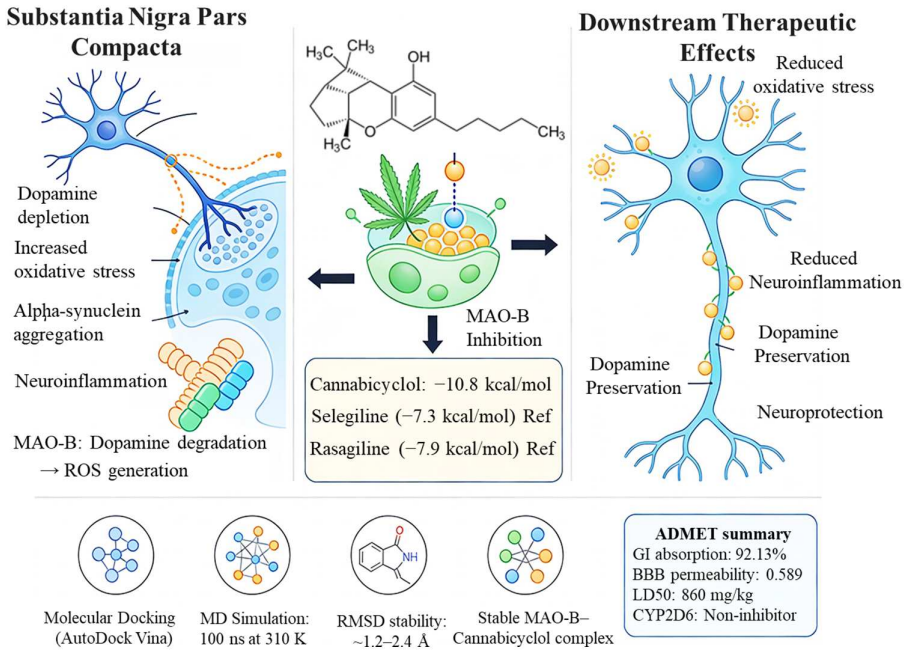

Figure 1. Graphical schematic illustrating the neuroprotective mechanism of *Cannabis sativa*–derived *Cannabicyclol* in Parkinson's disease through monoamine oxidase B (MAO-B) inhibition. (Parkinson's disease pathology is characterized by dopaminergic neuronal degeneration in the substantia nigra, leading to dopamine depletion, increased oxidative stress, α-synuclein aggregation, and neuroinflammation. *Cannabicyclol* binds to the active site of MAO-B with high affinity (docking score: −10.8 kcal/mol), outperforming reference inhibitors selegiline and rasagiline, thereby inhibiting dopamine degradation and reducing reactive oxygen species (ROS) generation. This interaction stabilizes the MAO-B–Cannabicyclol complex, as supported by molecular dynamics simulations (100 ns at 310 K; RMSD 1.2–2.4 Å) and favorable ADMET properties. Collectively, MAO-B inhibition results in dopamine preservation, reduced oxidative stress and neuroinflammation, enhanced neuronal survival, and improved motor function).

drug-likeness, toxicity, and ADMET profiles to determine the safety and efficacy of these compounds as potential candidates for PD treatment.

2. In Silico Experiment Design

2.1. Ligand selection and structural preparation

A total of 14 bioactive compounds derived from *Cannabis sativa* were selected based on a comprehensive review of current scientific literature highlighting their medicinal and neuroprotective potential. The chemical structures of the selected ligands were retrieved in Structure Data File (SDF) format from two widely used chemical databases: PubChem (https://pubchem.ncbi.nlm.nih.gov/) and ZINC (https://zinc.docking.org/substances/home/). These databases provided access to high-quality, three-dimensional structural data essential for computational analysis. Following retrieval, all ligand structures were subjected to energy minimization using *UCSF Chimera X*. This process ensured the removal of steric clashes, optimized geometry, and prepared the ligands for accurate molecular docking by converting them into their most stable conformational states. The minimized structures were then saved in a compatible format for subsequent docking simulations.

2.2. Protein structure retrieval and preparation

The three-dimensional crystal structure of human MAO-B (PDB ID: 2C65) was retrieved from the RCSB Protein Data Bank. MAO-B plays a critical role in the pathophysiology of PD by catalyzing the oxidative deamination of dopamine, a process that generates hydrogen peroxide and reactive oxygen species, ultimately leading to dopaminergic neuronal loss [32, 33]. Structurally, the MAO-B active site is organized into three distinct functional domains: an entrance cavity (~290 $Å^3$), a substrate-binding pocket (~490 $Å^3$), and a catalytic "aromatic cage" [34, 35]. These cavities are separated by a dynamic gating loop comprising Phe168, Leu171, Ile199, and Tyr326, with Ile199 functioning as a conformational "gate" that regulates ligand access to the substrate cavity [36, 37]. The aromatic cage, essential for substrate orientation and catalysis, is formed by the flavin-adenine dinucleotide (FAD) cofactor and residues Tyr398 and Tyr435 [38].

Given its central involvement in disease progression and well-characterized binding architecture, MAO-B was selected as the primary target for this study. Prior to computational analysis, the crystal structure was pre-processed using UCSF ChimeraX to remove co-crystallized ligands, water molecules, and other non-essential heteroatoms. Hydrogen atoms were added to complete residue valency, and energy minimization was performed to eliminate steric clashes and stabilize the molecular geometry. The optimized structure was subsequently saved in a docking-compatible format for downstream molecular docking and simulation studies.

2.3. ADMET profiling and drug-likeness assessment

The evaluation of ADME/T (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties was conducted to minimize the risk of compound failure during later stages of drug development. Computational tools SwissADME (https://www.swissadme.ch) and pkCSM (https://biosig.lab.uq.edu.au/pkcsm/) were used to assess critical pharmacokinetic parameters [39].

These included molecular weight, lipophilicity (log P), hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), topological polar surface area, number of rotatable bonds (nRotB), and compliance with Lipinski's Rule of Five. The analysis provided vital insights into the oral absorption, tissue distribution, metabolic stability, and potential toxicity of the selected compounds. Most compounds demonstrated favorable gastrointestinal absorption and the ability to penetrate the blood-brain barrier (BBB), making them promising candidates for neurological applications. Additionally, the compounds exhibited high metabolic stability and low predicted toxicity, ensuring safety for further exploration. This systematic prediction highlights the potential of the selected compounds as viable therapeutic candidates, guiding their prioritization for subsequent experimental validation and preclinical studies.

2.4. In silico toxicity prediction

The toxicity of the selected compounds was assessed using the ProTox-II database (https://tox-new.charite.de/protox_II/), a robust computational tool for predicting potential toxicological properties [40]. The analysis focused on calculating the LD50 values (median lethal dose) and assigning compounds to specific toxicity classes based on their predicted profiles. This systematic evaluation enabled the identification of compounds with lower predicted toxicity, facilitating the selection of safer therapeutic candidates. By prioritizing compounds with favorable toxicity profiles, the process ensures the development of treatment options with minimal adverse effects, thereby enhancing their suitability for further preclinical and clinical investigations.

2.5. Biological activity spectrum analysis of Cannabicyclol

The biological activity spectrum of Cannabicyclol was predicted using the PASS online platform (https://www.way2drug.com/PassOnline/) [41]. This in silico approach provided valuable insights into the compound's potential mechanisms of action and its therapeutic relevance for PD. The prediction was based on Multilevel Neighborhoods of Atoms descriptors, which highlight the influence of the compound's chemical structure on its biological activities. These results contribute to understanding Cannabicyclol's pharmacological profile and support its further investigation as a candidate for PD treatment.

2.6. Molecular docking protocol and validation

The Lamarckian genetic algorithm was used to perform the molecular docking study with the PyRx-v0.8 virtual screening tool utilizing AutoDock-Vina. A total of 14 phytochemical ligands derived from *Cannabis sativa* were docked individually with the MAO-B protein structure (PDB ID: 2C65). The enzyme was prepared as a macromolecule, and each ligand was loaded separately for analysis. The docking grid box was centered at the active site of MAO-B, with coordinates set to x = 53.9113, y = 149.558, and z = 17.1728, ensuring accurate targeting of the binding pocket. To facilitate post-docking analysis, the 2D and 3D interactions between ligands and the enzyme were visualized using BIOVIA Discovery Studio v21.1.0. This enabled identification of the key amino acid residues involved in ligand binding, characterization of bonding interactions, and evaluation of binding conformations. To benchmark the docking performance of the cannabis-derived compounds, known MAO-B inhibitors Deprenyl, Rasagiline, and Selegiline were used as reference standards, displaying binding affinities of −7.3 kcal/mol, −7.9 kcal/mol, and −7.3 kcal/mol, respectively. These reference compounds served as baselines for comparative evaluation of the docking efficiency of the test ligands [42]. The asymmetric unit of PDB entry 2C65 contains two identical protein chains (Chain A and Chain B), each comprising 520 amino acid residues. Both chains harbor a complete active site with bound FAD cofactor and the co-crystallized inhibitor ligand (4CR). For computational consistency and to enable protocol validation via redocking of the native ligand, Chain A was explicitly selected for all docking and MD simulations. This selection aligns with standard practice in structure-based drug design studies of MAO-B, where Chain A is conventionally used due to its complete electron density, optimal ligand occupancy, and precedent in prior crystallographic and computational investigations of MAO-B inhibitors [43]. Molecular docking validation was performed by extracting the co-crystallized 4CR ligand and redocking the co-crystallized ligand on the active site coordinates of MOA-B. Finally, the redock pose was superimposed on the bound ligand, and root mean square deviation (RMSD) was calculated using Discovery Studio. Protocol validation via redocking of co-crystallized ligand 4CR yielded RMSD = 1.382 Å (see Results for details).

2.7. Molecular dynamics simulation setup and analysis

Desmond was used for the MD simulation https://www.schrodinger.com/products/desmond. In this study, the MAO-B protein and Cannabicyclol molecule with the highest molecular docking score for MD simulation analysis were selected. We ran the simulation at 310 Kelvin for 100 ns. An orthorhombic box with dimensions of 10 nm × 10 nm × 10 nm was generated. The forcefield Optimized Potentials for Liquid Simulations-3e was applied to the single point charge water model to solve the system. In total, 53,853 atoms and 15,255 water molecules were present in the system. To maintain stability, we applied an ensemble known as NPT, combined with a Nose-Hoover thermostat and barostat. The graphs were generated presenting the RMSD and root mean square fluctuation (RMSF), which helped us understand how the shape of the complex changes with time and better understand its behavior.

3. Results and Discussion

3.1. Basic physicochemical premises of cannabis compounds

The physicochemical properties of the fourteen selected cannabis compounds were evaluated according to Lipinski's Rule of Five, revealing a generally favorable profile for drug-likeness, with most compounds meeting the key criteria for molecular weight, rotatable bonds, and HBD/HBA (Table 2). While there was one violation for compounds such as Cannabicyclol, Cannabinol, Cannabicitran, Cannabivarin, Cannabigerol, Cannabidiol, and Cannabinodiol, the compounds still demonstrated promising characteristics for therapeutic potential. Molecular weights ranged from 282.4 to 370.57 g/mol, with logP values ranging from 3.9552 to 6.0657, indicating moderate lipophilicity, which is essential for crossing biological membranes and potentially the BBB. The nRotB varied from 2 to 12, impacting molecular flexibility, which is important for receptor binding. HBD and HBA were well-balanced for most compounds, with

Table 2. The physicochemical properties of 14 selective compounds

Compound names	Molecular weight g/m	Rotatable bonds	H-bond donor	H-bond acceptor	Lipinski violation	Log p
Cannabicyclol	314.5	4	1	2	1	5.4256
Cannabitriol	346.5	4	3	4	0	3.9552
Cannabinol	310.5	4	1	2	1	5.7278
Cannabicitran	350.75	4	0	2	1	5.6251
Cannabivarin	282.4	2	1	2	1	4.9476
Cannabigerol	316.5	9	2	2	1	6.0657
Cannabidivarin	296.5	4	2	2	0	5.0663
Cannabidiol	314.5	6	2	2	1	5.8465
Cannabigerolic Acid	370.57	12	3	4	0	4.8680
Cannabinodiol	348.73	6	2	2	1	5.8390
Cannabielsoin	330.5	5	2	3	0	4.7066
Delta (9)- Tetrahydrocannabinolic Acid	358.47	5	2	4	0	5.434
Tetrahydrocannabinol	314.5	4	1	2	1	5.7358
Tetrahydrocannabivarin	286.41	2	1	2	0	4.9556

values ranging from 0 to 3 for donors and 2–4 for acceptors. These results suggest that the selected cannabis compounds are likely to exhibit favorable pharmacokinetic properties, making them viable candidates for further investigation as therapeutic agents for neurodegenerative diseases such as PD.

3.2. ADMET and toxicity appraisal

The ADMET parameters and toxicity profiles of the selected cannabis compounds were evaluated using the PkCSM and SWISS-ADME web servers. All compounds demonstrated high gastrointestinal absorption, ranging from 85.95% to 94.46%, indicating strong oral bioavailability, which is crucial for effective drug delivery. BBB permeability varied across the compounds, with Cannabicyclol and Cannabinol showing moderate permeability (0.589 and 0.771, respectively), while others like Cannabigerol and Cannabidivarin had limited BBB permeability, potentially affecting their ability to target central nervous system (CNS) diseases. CNS permeability values also indicated a limited ability to cross into the brain for most compounds. The predicted LD50 values ranged from 482 mg/kg for Tetrahydrocannabinol to 13,500 mg/kg for Cannabinol, placing all compounds in toxicity class IV or higher, signifying low acute toxicity. Furthermore, none of the compounds showed significant interaction with CYP 2D6, suggesting a reduced risk of metabolic interference with other drugs (Figure 2). Drug-likeness profile of Cannabicyclol based on Lipinski's Rule of Five. Parameters are mentioned in Figure 3. These results, as detailed in Table 3, underscore the cannabis compounds' promising pharmacokinetic profiles and low-to-moderate toxicity, positioning them as viable candidates for further development in treating neurodegenerative diseases like PD with minimal adverse effects.

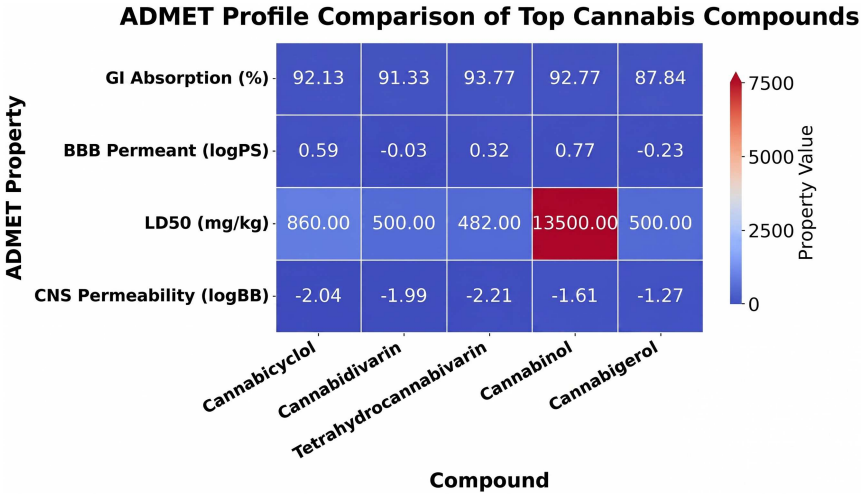

Figure 2. Comparative ADMET properties of top five cannabis constituents. GI absorption (%), BBB permeability (logPS), LD_{50} (mg/kg), and CNS permeability (logBB) are shown. Cannabinol demonstrates exceptional safety (LD_{50} = 13,500 mg/kg), while Cannabicyclol shows favorable BBB penetration (logPS = 0.589). Color scale reflects property magnitude (red = high/favorable, blue = low/less favorable)

Table 3. ADMET parameters and toxicity prediction of the compounds

Compound	GI absorption	BBB permeant	CNS permeability	Predicted LD50 mg/kg	CYP 2D6	Toxicity Class
Cannabicyclol	92.13	0.589	–2.041	860	No	4
Cannabitriol	85.95	–0.73	–2.206	750	No	4
Cannabinol	92.77	0.771	–1.606	13500	No	4
Cannabicitran	89.76	0.413	–2.148	860	No	4
Cannabivarin	93.16	0.646	–1.62	13500	No	6
Cannabigerol	87.84	–0.225	–1.268	500	No	4
Cannabidivarin	91.33	–0.027	–1.988	500	No	4
Cannabidiol	90.65	–0.113	–1.886	500	No	4
Cannabigerol acid	94.46	–1.084	–2.707	4600	No	5
Cannabinodiol	91.47	–0.102	–1.547	1500	No	4
Cannabielsoin	91.97	–0.131	–1.962	500	No	4
Delta (9)-Tetrahydrocannabinolic Acid	98.08	–0.124	–1.948	500	No	4
Tetrahydrocannabinol	93.09	0.448	–2.104	482	No	4
Tetrahydrocannabivarin	93.77	0.32	–2.206	482	No	4

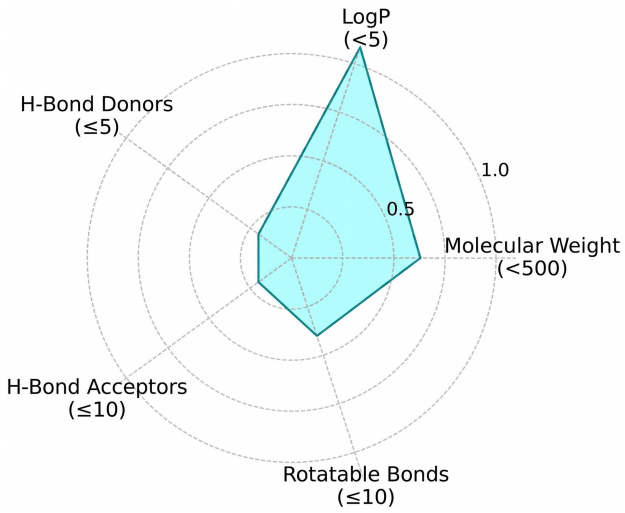

Figure 3. Drug-likeness profile of Cannabicyclol based on Lipinski's Rule of Five. Parameters normalized to ideal thresholds: Molecular Weight (<500 Da), LogP (<5), H-bond donors (≤5), H-bond acceptors (≤10), Rotatable bonds (≤10). Values >1 indicate deviation from ideal; Cannabicyclol complies with all rules except LogP (5.43), which is marginally above threshold

3.3. Bioactive spectra prediction for Cannabicyclol

The bioactive spectra of Cannabicyclol were predicted using the PASS platform, which assessed the probabilities of biological activity (Pa) and inactivity (Pi). The results in Table 4 show that Cannabicyclol has high activity probabilities for neurotrophic factor enhancement (Pa = 0.580), immunosuppression (Pa = 0.571), and neuromuscular inhibition (Pa = 0.496), suggesting potential for treating neurodegenerative diseases. Other predicted activities include cytoprotection, chemoprevention, and anti-inflammatory effects, highlighting its broad therapeutic potential. These findings support Cannabicyclol as a promising candidate for further development in neurodegenerative disease treatments.

Table 4. PASS prediction results for the biological activities of the top-performing docked ligand (Cannabicyclol)

Biological activities	Pa	Pi
Neurotrophic factor enhancer	0.580	0.003
Immunosuppressant	0.571	0.033
Neuromuscular inhibiting agent for acetylcholine	0.496	0.077
Cytoprotectant	0.421	0.088
Chemopreventive	0.410	0.021
Treatment for acute neurological conditions	0.405	0.139
Kinase inhibitor	0.394	0.069
Anti-inflammatory	0.242	0.222
Protein synthesis blocker	0.184	0.062
TP53 expression enhancer	0.622	0.043

3.4. Molecular docking reveals superior binding of Cannabicyclol to MAO-B

Molecular docking simulations were conducted using AutoDock, with docking scores reported in negative values, where more negative binding energies indicate stronger binding affinities and potentially higher inhibitory potency [44]. All 14 *Cannabis sativa*-derived ligands were successfully docked to the MAO-B protein, and their binding affinities were systematically evaluated. Compounds were ranked based on their binding energy, with lower (more negative) values representing stronger interactions with the target enzyme. Among the tested ligands, the top four exhibiting the most favorable docking scores were selected for further analysis. As summarized in Table 5, the binding affinities of the ligands ranged from −6.1 to −10.8 kcal/mol. Notably, Cannabicyclol exhibited the strongest binding interaction with MAO-B, achieving a docking score of −10.8 kcal/mol. This value is significantly lower than those observed for standard reference inhibitors such as *Deprenyl* and Selegiline (−7.3 kcal/mol each), indicating a potentially higher inhibitory potency. These results suggest that selected *Cannabis sativa* phytochemicals, particularly

Table 5. Binding affinities (kcal/mol) of cannabis compounds against selected target proteins

Compounds	kcal/mol
Cannabicyclol	–10.8
Cannabitriol	–7.7
Cannabinol	–9.6
Cannabicitran	–9.1
Cannabivarin	–9.6
Cannabigerol	–9.1
Cannabidivarin	–9.1
Cannabidiol	–8.4
Cannabigerolic acid	–9.4
Cannabinodiol	–8.5
Cannabielsoin	–5.8
Delta (9)-Tetrahydrocannabinolic Acid	–8.9
Tetrahydrocannabinol	–9.3
Tetrahydrocannabivarin	–9.2

Cannabicyclol, may serve as potential candidates for further development as MAO-B inhibitors in the treatment of PD.

3.5. Molecular interaction of the MAO-B active residues with the highest docking score compounds

The top four cannabis ligands, Cannabicyclol (−10.8 kcal/mol), *Cannabinol* (−9.6 kcal/mol), *Tetrahydrocannabinol* (−9.2 kcal/mol), and *Cannabidivarin* (−9.6 kcal/mol), demonstrated significantly higher binding affinities for MAO-B compared to the baseline MAO-B inhibitors Deprenyl (−7.3 kcal/mol), Rasagiline (−7.9 kcal/mol), and Selegiline (−7.3 kcal/mol), which were used to assess the efficacy of MAO-B receptor analogs [42]. These findings, visualized in Figure 4 and summarized in Table 6, highlight the superior binding stability of the cannabis compounds. Cannabicyclol, with the highest docking score, forms two hydrogen bonds with Cys172 and Tyr435, while also engaging in extensive vander Waals interactions with key residues such as Gly58, Ser59, Tyr188, and Gln206. *Cannabidivarin* forms hydrogen bonds with Cys397 and interacts with various residues via vander Waals forces. These molecular interactions are crucial for MAO-B inhibition, underscoring the therapeutic potential of these cannabis compounds for treating neurodegenerative diseases like PD.

Cannabicyclol, a bioactive compound derived from *Cannabis sativa*, demonstrates a strong binding affinity to MAO-B with a molecular docking score of −10.8 kcal/mol, outperforming standard MAO-B inhibitors such as Deprenyl and Selegiline (−7.3 kcal/mol). This interaction involves the formation of two hydrogen bonds with key residues Cys172 and Tyr435, along with extensive vander Waals interactions with Gly58, Ser59, Tyr188, and Gln206. These results suggest that *Cannabicyclol* not only binds effectively at the MAO-B active site but also stabilizes the enzyme in a conformation that may inhibit its catalytic activity, crucial for dopamine degradation in PD. Given its high binding affinity, *Cannabicyclol* holds significant potential as an MAO-B inhibitor, presenting a potential alternative to existing treatments with a reduced risk of side effects, warranting further investigation in PD therapy. The interaction between Cannabicyclol and MAO-B is presented in Figure 5, which highlights the key binding interactions and MD. These computational results

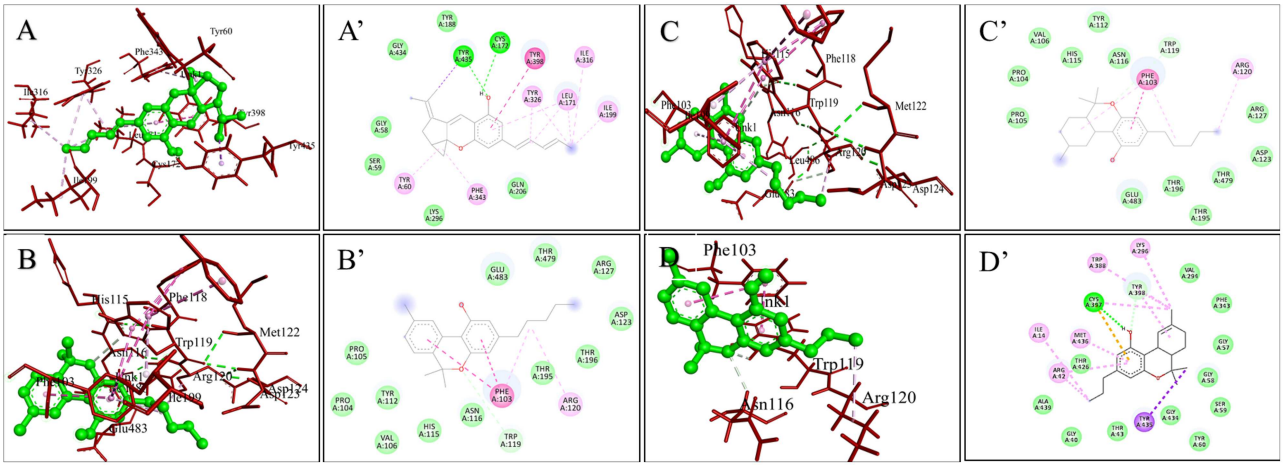

Figure 4. 3D (Left) and 2D (right) views of interacting residues of MAO-B with the four highest score compounds: (A, A') Cannabicyclol, (B, B') *Cannabinol*, (C, C') *Tetrahydrocannabinol* (D, D') *Cannabivarin*

Table 6. Shows the interaction of top selected compounds with MAO-B protein residues

Compound	Binding energy (kcal/mol)	H-bonds interacting	Vander Waals interactions
Cannabicyclol	−10.8	Cys172, Tyr435	Gly58, Ser59, Tyr188, Ile199, Gln206, Lys296
Cannabinol	−9.6	0	Gly57, Gly58, Ser59, Leu164, Cys172, Ile198, Gln206, Lys296, Ile316, leu320, Met341, Tyr435
Tetrahydro-cannabinol	−9.3	0	Gly40, THr43, Gly57, Gly58, Ser59, Tyr60, Phe343, Val294, Tyr398, Thr426, Gly434, Ala439
Cannabivarin	−9.6	CYS397	Thr43, Gly57, Gly58, Ser59, Tyr188, Lys296, Thr426, Gly434

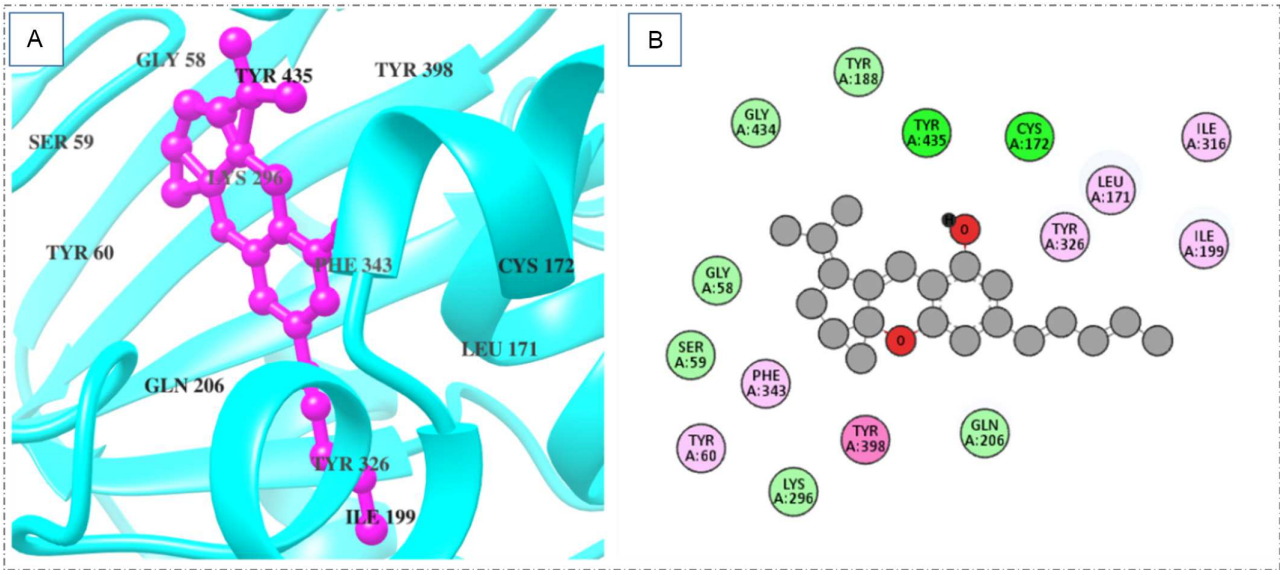

Figure 5. Molecular docking of Cannabicyclol with MAO-B. (A) Overall structure showing Cannabicyclol in pink at the active site, highlighting key residues including Gly58, Tyr435, and Cys172. (B) 2D interaction network showing the key binding residues involved in the interaction

suggest that Cannabicyclol is predicted to bind effectively at the MAO-B active site and may stabilize the enzyme in a conformation that could potentially inhibit its catalytic activity, though this requires experimental confirmation.

3.6. Validation of docking protocol

The molecular docking protocol used for cannabinoid binding against monoamine oxidase B (MAO-B) was validated through a redocking experiment using the co-crystallized reference ligand (4CR) in the active site of the structure (PDB ID: 2C65). The redocked pose (cyan) has a good spatial overlap of the experimentally solved bound conformation (orange); as shown by the superimposition analysis, the employed docking parameters are able to reliably reproduce the native binding pose of the ligand in the catalytic cavity. The RMSD was 1.382 Å, which is well below the validation threshold of 2.0 Å (Figure 6). Therefore, we can be assured of the reliability of the docking workflow. The redocked ligand also obtained a docking score of −8.319 kcal/mol, indicating a strong binding affinity along with being consistent with the experimental value of the ligand–protein complex. The similarity in geometrical properties of the two poses strongly suggests that this protocol is suitable for the docking of cannabinoids and comparative reference ligands against MAO-B.

The redocking method was confirmed as valid using the two-dimensional interaction profile as the key ligand–residue contacts were conserved with those in the crystal. Importantly, the interactions with Cys172 and Gln206 of the redocked conformation show that the recognition pattern at the active site was reproduced. The stability of the ligand as a result of the same polar and/or hydrophobic contacts that underlie conservation is important for correct pose prediction. Additional neighboring residues, especially hydrophobic amino acids around the binding pocket, presented a similar environment and sustained fidelity of the docking model. Being low in value, the RMSD score, docking score, good superimposition with the native pose, and similarity with the native pose in respect of important interactions confirm that the docking protocol is valid and a sufficiently reliable tool to study the binding behavior of cannabinoid analogs in the MAO-B active site. It can be concluded that subsequent docking results could be interpreted as mechanistically relevant in the present study for structure-based inhibitor design and binding mode analysis.

3.7. Molecular dynamics confirms stability of the Cannabicyclol–MAO-B complex

3.7.1. Root mean square deviation (RMSD)

RMSD provides information about the fluctuation of the protein structure relative to its reference structure. For the first 23 ns of the simulation, the ligand had a relatively stable RMSD of 0.8 Å. This demonstrates that the ligand retained its stable conformation during this time. However, the ligand underwent a sudden conformational change at 23 ns, which caused a higher RMSD value of 2.8 Å over the remaining 100 ns. This shows that after 23 ns, the ligand underwent another significant structural rearrangement or binding event with the protein, leading to a new stable conformation with higher structural divergence from the initial state. According to the RMSD values, the protein undergoes structural variation during the first 23 ns, which fluctuates from 1.2 Å to 2.4 Å. This suggests that the protein is already flexible or that it is undergoing structural changes. However, the protein became more stable after 23 ns in the remaining 100 ns. This suggests that the protein becomes stable after the minor fluctuations and maintains this stable conformation till the end of the simulation (Figure 7A).

3.7.2. Root mean square fluctuation (RMSF)

RMSF is a measure used to quantify the fluctuation or flexibility of atoms or residues within a biomolecular system over time. The RMSF values were in the range of 0.6 Å to 1.2 Å; most protein residues typically undergo minor fluctuations during the simulation. Lower RMSF values (closer to 0.6) in a residue signify structurally stable protein regions that have not significantly changed from their initial conformation. These regions might

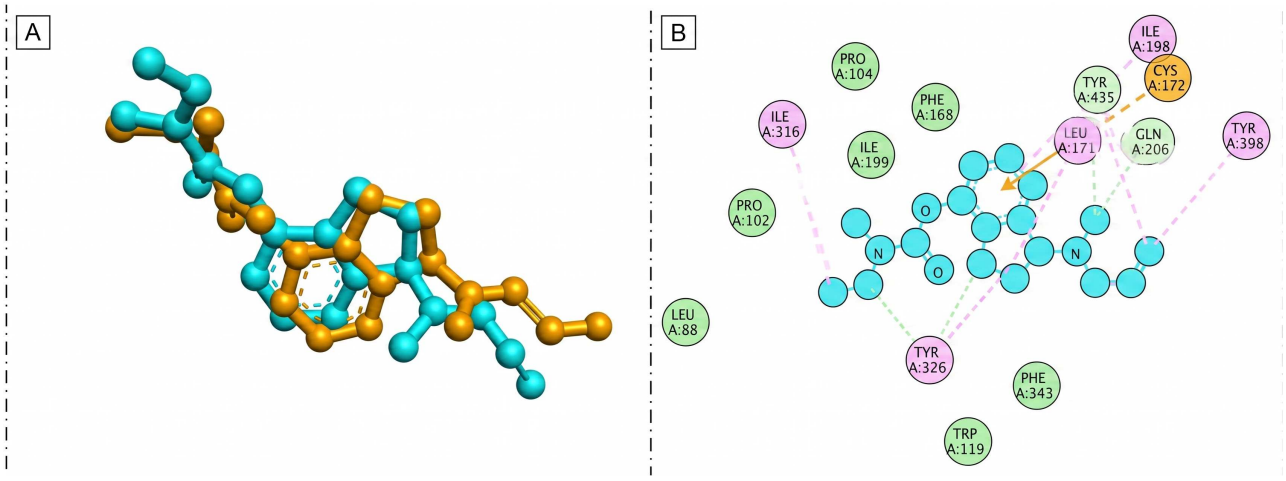

Figure 6. Docking protocol validation for MAO-B. (A) Superimposition of native (orange) and redocked (cyan) poses of the reference ligand 4CR (RMSD = 1.382 Å). (B) 2D map showing conserved interactions of the redocked ligand with key active site residues, including Cys172 and Gln206

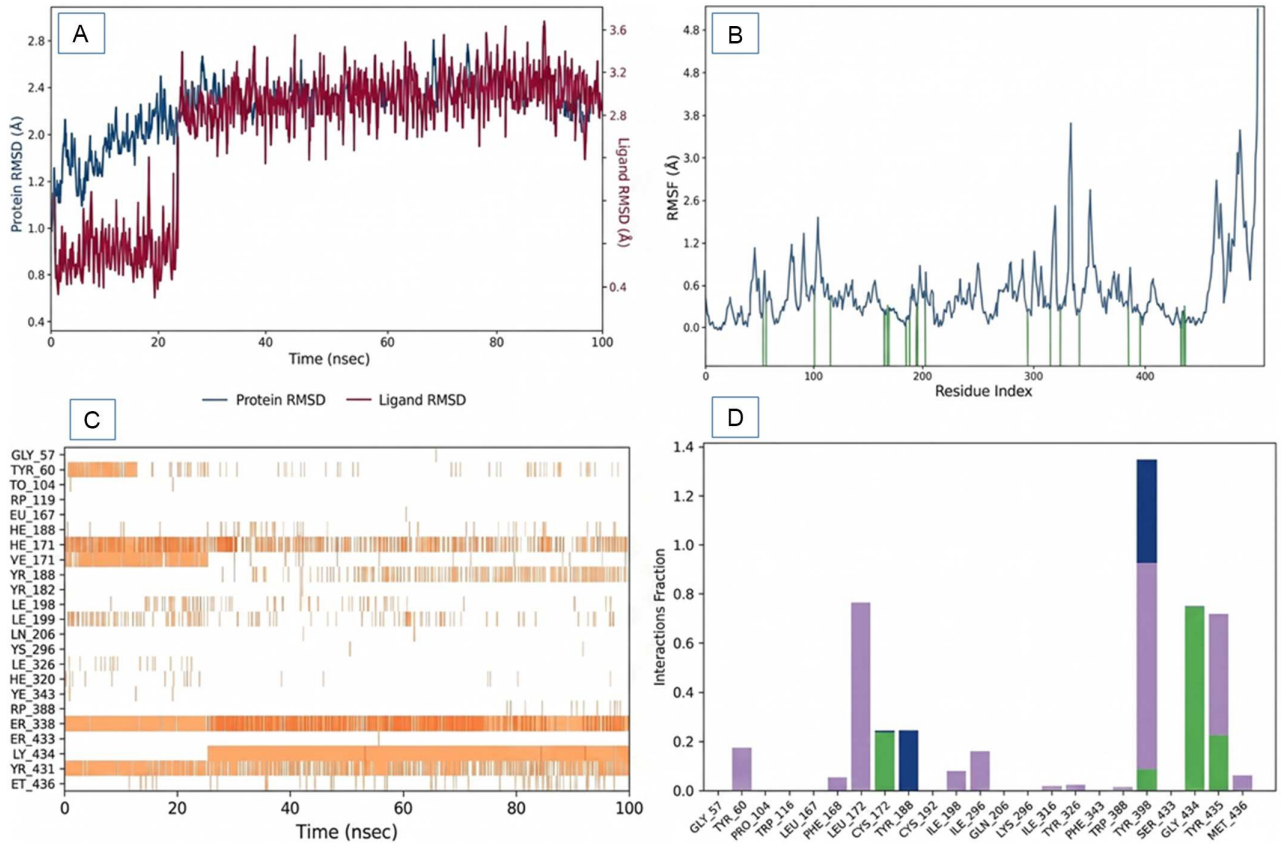

Figure 7. MD simulation studies of the selected protein ligand complex, 7A) RMSD of the protein ligand complex, 7B) RMSF of the targeted protein indicating fluctuating residues during the simulation timeperiod, 7C) interaction between the ligand and protein residues, 7D) Hydrogen bonds between the protein and ligand during simulation timeperiod

correlate with stable secondary structures with high order, such as alpha helices or beta sheets. During the simulation, some residues or regions experienced minor fluctuations, as indicated by the RMSF peaks higher than 1.2 Å. These more flexible portions of the protein may correspond to loops, turns, or other, more flexible locations. The higher RMSF values indicate that these regions are more dynamic and are probably subject to local movements or conformational changes throughout the simulation (Figure 7B).

3.7.3. Ligand–protein contact

The ligand–protein contact analysis reveals that Cannabicyclol interacts with 25 protein residues, from Gly57 to Met436, through a variety of interactions including hydrogen bonds

(H-bonds), water bridges, and hydrophobic and ionic bonds. The H-bonds are essential for ligand binding and drug selectivity, and they include backbone and side-chain donors and acceptors. Additionally, hydrophobic interactions, such as π-cation and π–π stacking, as well as nonspecific interactions with hydrophobic amino acids, play a role in stabilizing the complex. Figure 7C and D show the time evolution of these interactions, highlighting the frequency and strength of binding between Cannabicyclol and MAO-B, underscoring its potential as a potential MAO-B inhibitor for PD treatment.

Principal component analysis (PCA) was utilized to examine the conformational changes in the MAO-B protein upon binding with Cannabicyclol. The analysis revealed that the first principal component (PC1), which accounts for 31.96% of the total variance, represents the most significant structural shifts. The blue and red clusters indicate regions of high and low flexibility in the protein structure, respectively. The second and third principal components (PC2 and PC3), explaining 11.81% and 8.11% of the variance, capture intermediate and minor fluctuations in the protein's conformation. The eigenvalue plot (Figure 8) highlights that the first few components account for the majority of the variance, emphasizing their role in understanding the protein–ligand interaction. These results suggest that Cannabicyclol binding primarily influences specific regions of the MAO-B protein, increasing flexibility in some areas while maintaining structural stability in others. The PCA findings, as shown in Figure 8, underscore the effectiveness of this method in revealing the dynamic conformational changes during the protein–ligand interaction in the context of PD.

The dynamic cross-correlation map shown in Figure 9 illustrates the inter-residual motions of the MAO-B protein, which is involved in PD, docked with Cannabicyclol. Cyan regions represent strong positive correlations between Cα atoms, indicating areas of stability and tightly coordinated movements essential for protein function. Magenta regions, representing negative correlations, highlight regions with less coupled or more flexible motions, which could be involved in conformational changes upon binding. Notably, residues 100–200 and 300–450 show significant positive correlations, likely corresponding to the active binding site regions. Overall, the map demonstrates the balance between structural integrity and flexibility within the MAO-B protein, with positively correlated regions indicating stability and negatively correlated regions suggesting areas that may undergo functional adaptability during the interaction with Cannabicyclol.

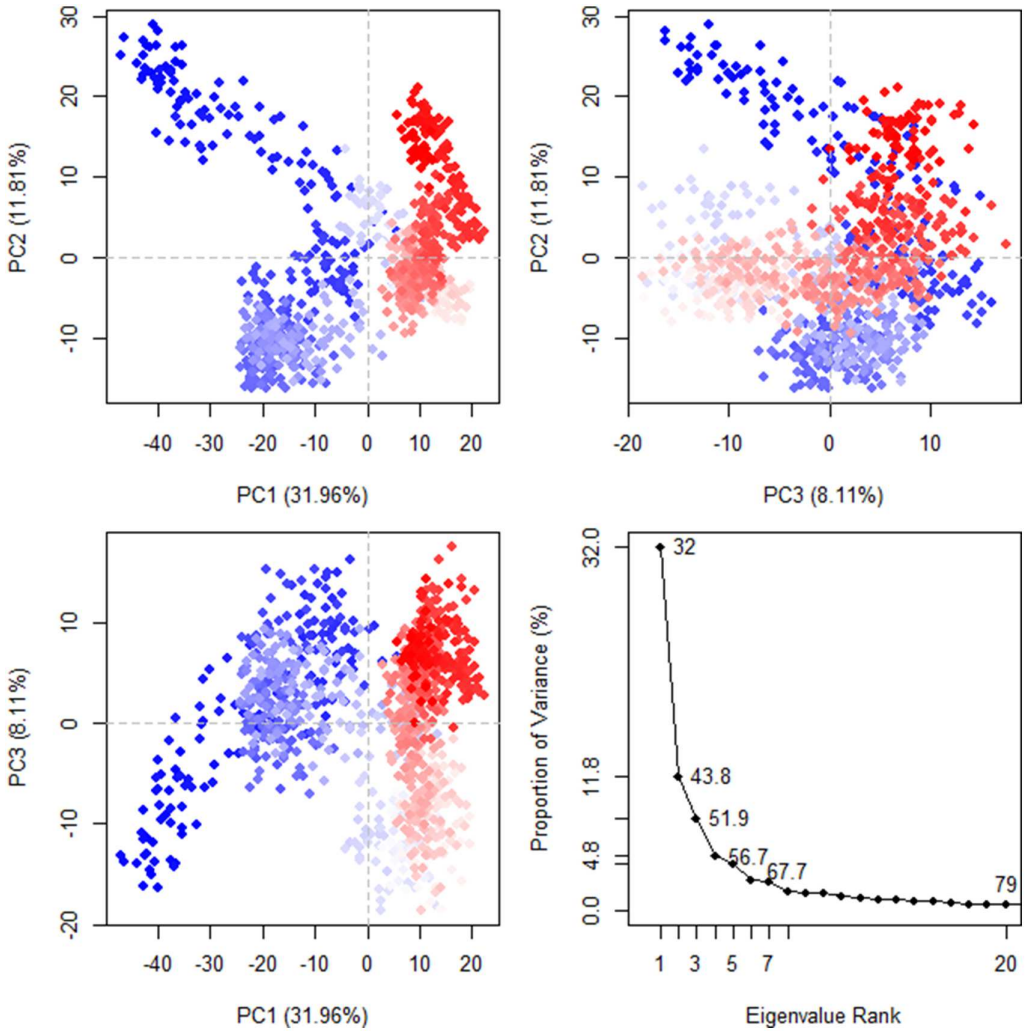

Figure 8. PCA analysis of the MAO-B protein-Cannabicyclol complex, showing significant conformational changes. PC1 accounts for 31.96% of the variance, while PC2 and PC3 explain 11.81% and 8.11%, respectively. The analysis highlights the flexibility changes induced by *Cannabicyclol* binding in specific regions of the protein.

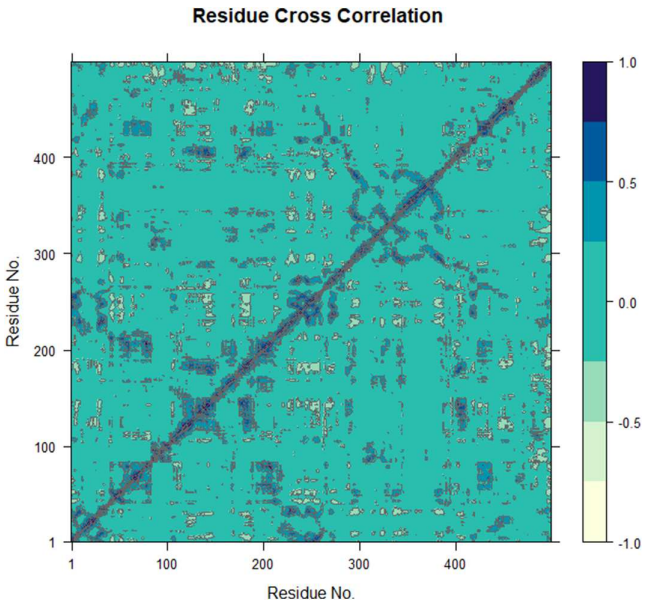

Figure 9. Residue cross-correlation map showing the inter-residual motions of the MAO-B protein. Cyan regions indicate strong positive correlations between Cα atoms, suggesting stable and coordinated movements, while magenta regions represent negative correlations, highlighting areas of flexibility and less coordinated motion.

4. Discussion

The present study aimed to perform molecular docking experiments to investigate the therapeutic potential of certain cannabis constituents for the treatment of PD. The focus was on identifying cannabis-derived compounds that could inhibit MAO-B, a key enzyme involved in the degradation of dopamine. By targeting MAO-B, the study aimed to explore how cannabis constituents might provide neuroprotective benefits and alleviate motor symptoms in PD patients. The findings revealed that Cannabicyclol, a cannabinoid derived from *Cannabis sativa*, exhibited a strong binding affinity for MAO-B, with a molecular docking score of −10.8 kcal/mol, surpassing the binding affinities of conventional MAO-B inhibitors such as Deprenyl and Selegiline. This suggests that Cannabicyclol may be a potential alternative treatment for PD.

Among the selected compounds, several are classified as phytocannabinoids, including types such as delta-9-tetrahydrocannabinol (Δ9-THC), delta-8-tetrahydrocannabinol (Δ8-THC), cannabigerol (CBG), cannabichromene (CBC), cannabidiol (CBD), cannabinodiol (CBND), cannabielsoin (CBE), cannabicyclol (CBL), and cannabitriol (CBT). Additionally, a number of non-cannabinoid derivatives are also found in *Cannabis sativa*, including flavonoids, nitrogenous compounds, xanthones, steroids, and fatty acids [45, 46]. These substances are utilized in medicine to treat or alleviate symptoms such as pain, spasticity, nausea, and vomiting. The endocannabinoid system appears to play a significant role in offering beneficial properties for the treatment of PD. In the present study, the analysis focuses on the computational prediction of MAO-B inhibition. MAO-B is a well-established target associated with dopaminergic neuroprotection, and its inhibition is a recognized strategy in the management of PD-related symptoms. However, it is important to emphasize that the findings reported here are based solely on in silico approaches and therefore represent preliminary predictions rather than experimentally validated biological effects [47, 48].

Clinical studies have shown that the endocannabinoid system experiences noticeable changes in its neurochemical and neurophysiological functions following a reduction in dopamine levels [49–52]. Due to a decrease in dopaminergic transmission, there is an increase in endocannabinoid levels and CB1 receptor expression in the basal ganglia [53]. This suggests that cannabinoids may have a therapeutic effect in treating movement abnormalities associated with PD. Furthermore, research has demonstrated that CBD has the ability to reduce the decrease in dopamine levels and thyroid hormone deficiencies, which are markers of the extent of neurodegeneration in the nigrostriatal dopaminergic projections [50]. The cannabinoids have the ability to decrease oxidative stress, making them potential neuroprotective agents in PD. Recent research underscores the significance of factors such as the frequency and duration of cannabinoid consumption, as well as the age of consumers, in influencing the overall health outcomes [54]. Hence, research on pathways associated with PD and related enzyme regulatory studies is essential. It has been demonstrated that cannabinoids reduce oxidative stress and excitotoxicity and control dopamine levels [55].

Currently, the management of PD involves several medications, including carbidopa, levodopa, anticholinergics, dopamine agonists, MAO-B inhibitors, catechol-O-methyltransferase inhibitors, and amantadine [56, 57]. Among these, levodopa is the most commonly prescribed, but it is often associated with side effects and long-term complications, presenting challenges in effective disease management [58]. To explore the therapeutic potential of cannabis-derived compounds, this study compared their binding affinities and interactions with levodopa and Citronellal. Recent studies have shown that Citronellal (CTN) has a binding affinity of −6.5 kcal/mol toward MAO-B, suggesting its potential for PD treatment. In our study, Cannabicyclol exhibited a more favorable docking score of −10.8 kcal/mol when interacting with MAO-B, indicating a stronger potential to inhibit the enzyme compared to Citronellal. These findings suggest that Cannabicyclol may be a potential multi-target therapeutic agent for PD, offering improved binding affinity and efficacy. Furthermore, the pharmacological properties of Cannabicyclol, including its ability to pass the BBB and its strong gastrointestinal absorption, support its potential for effective therapeutic use. When compared to established MAO-B inhibitors such as Deprenyl, Rasagiline, and Selegiline, Cannabicyclol, along with other cannabis compounds like Cannabitriol, Cannabivarin, Cannabinol, and Cannabicitran, showed superior binding affinities and interactions with the MAO-B enzyme [59, 60]. The favorable physicochemical properties of these cannabis constituents, such as moderate molecular weight, lipophilicity, and ADME/T profiles, enhance their suitability as potential drug candidates for PD treatment, necessitating further preclinical and clinical studies to validate their therapeutic efficacy [61, 62].

This in silico study demonstrates that several newly identified cannabis-derived compounds exhibit stronger binding affinities for key enzymes, indicating their potential as therapeutic candidates compared to previous studies. Specifically, our molecular docking analysis supports the viability of Cannabicyclol as a potential candidate for the treatment of PD. The compound's favorable physicochemical properties, anticipated ADME/T profiles, and interactions with target proteins suggest it could offer significant therapeutic benefits [63]. Given these findings, Cannabicyclol warrants further investigation as a potential treatment for PD and other neurological disorders. To establish its clinical efficacy, future research should focus on in vitro and in vivo studies, followed by well-designed clinical trials. These results indicate that Cannabicyclol has the potential to serve as a multi-target therapeutic agent for PD. However, this study is purely computational.

Docking scores and MD stability metrics do not equate to experimental IC50 values or in vivo efficacy. Solubility, metabolic stability, and BBB permeability predictions require experimental validation. Future in vitro enzymatic assays and cell-based neuroprotection models are essential to confirm Cannabicyclol's MAO-B inhibitory activity.

5. Conclusion

This study highlights the potential of Cannabicyclol, a cannabinoid derived from *Cannabis sativa*, as a novel therapeutic agent for PD. Through molecular docking simulations and MD simulations, we identified that Cannabicyclol binds strongly to MAO-B, a crucial enzyme in the pathophysiology of PD. Its binding affinity, surpassing that of conventional MAO-B inhibitors like Deprenyl and Selegiline, suggests Cannabicyclol's potential to offer enhanced neuroprotective effects by preserving dopamine levels and reducing oxidative stress. In addition, its favorable physicochemical properties, such as moderate lipophilicity and ability to cross the BBB, further support its therapeutic promise. The study underscores the need for in-depth preclinical and clinical studies to assess Cannabicyclol's efficacy as a multi-targeted treatment for PD, ultimately contributing to the advancement of cannabis-derived therapies for neurodegenerative diseases.

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Ethical Statement

This study did not involve human participants or animal subjects. Therefore, ethical approval and informed consent were not required. All analyses were performed using publicly available data and in silico computational methods, with no human- or animal-derived experimental data used.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this work.

Data Availability Statement

The data that support this work are available upon reasonable request to the corresponding author.

Author Contribution Statement

Attiya Jamshaid: Methodology, Software, Investigation, Writing – original draft, Visualization. **Moawaz Aziz:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing – original draft, Visualization. **Usama Raza:** Methodology, Validation, Writing – review & editing. **Rahman Mazhar:** Formal analysis. **Muhammad Asad Ullah Shakil:** Data curation. **Muhammad Sajid:** Data curation. **Lixia Tang:** Resources, Writing – review & editing, Supervision. **Sheikh Arslan Sehgal:** Conceptualization, Resources, Writing – review & editing, Supervision, Project administration.

References

[1] Kakudidi, E., Tugume, P., Asiimwe, S., & Anywar, G. (2022). Traditional and modern Health uses of *Cannabis sativa L.* In Africa and its phytochemical and pharmacological profile. In D. C. Agrawal, R. Kumar, & M. Dhanasekaran (Eds.), *Cannabis/Marijuana for Healthcare* (pp. 189–210). Springer Nature Singapore. https://doi.org/10.1007/978-981-16-8822-5_10

[2] Corroon, J., & Kight, R. (2018). Regulatory status of cannabidiol in the United States: A perspective. *Cannabis & Cannabinoid Research*, *3*(1), 190–194. https://doi.org/10.1089/can.2018.0030

[3] Fidan, M., Süzerer, V., & Onay, A. (2023). *Cannabis sativa L.*: Origin, distribution, taxonomy and biology. *Türk Bilimsel Derlemeler Dergisi*, *16*(1), 10–28.

[4] Govindarajan, R. K., Mishra, A. K., Cho, K. H., Kim, K. H., Yoon, K. M., & Baek, K. H. (2023). Biosynthesis of phytocannabinoids and structural insights: A review. *Metabolites*, *13*(3), 442. https://doi.org/10.3390/metabo13030442

[5] Caprioglio, D., Amin, H. I. M., Taglialatela-Scafati, O., Muñoz, E., & Appendino, G. (2022). Minor phytocannabinoids: A misleading name but a promising opportunity for biomedical research. *Biomolecules*, *12*(8), 1084. https://doi.org/10.3390/biom12081084

[6] Avoseh, F. T., Mtunzi, F. M., Avoseh, O. N., & Takaidza, S. (2025). *Cannabis sativa*; ethnobotanicals, classifications, pharmacology, and phytochemistry. *Natural Product Communications*, *20*(6), 1934578X251334244. https://doi.org/10.1177/1934578X251334244

[7] Bhunia, S., Kolishetti, N., Arias, A. Y., Vashist, A., & Nair, M. (2022). Cannabidiol for neurodegenerative disorders: A comprehensive review. *Frontiers in Pharmacology*, *13*, 989717. https://doi.org/10.3389/fphar.2022.989717

[8] Vihal, S., Singh, V., Rana, R., & Kaur, S. D. (2026). Insights into cannabis and cannabinoids: Chemical properties, legal perspectives, and therapeutic applications. *Chemistry & Biodiversity*, *23*(3), e03030. https://doi.org/10.1002/cbdv.202503030

[9] Davis, M. P. (2022). Overview of the endocannabinoid system and endocannabinoidome. In C. Cyr, M. P. Davis, D. Schecter, & P. Daeninck (Eds.), *Cannabis and Cannabinoid-Based Medicines in Cancer Care* (pp. 1–40). Springer International Publishing. https://doi.org/10.1007/978-3-030-89918-9_1

[10] Kumar, P., Mahato, D. K., Kamle, M., Borah, R., Sharma, B., Pandhi, S., . . . , & Mishra, A. K. (2021). Pharmacological properties, therapeutic potential, and legal status of *Cannabis sativa L.*: An overview. *Phytotherapy Research*, *35*(11), 6010–6029. https://doi.org/10.1002/ptr.7213

[11] Prakash, S., & Carter, W. G. (2021). The neuroprotective effects of cannabis-derived phytocannabinoids and resveratrol in parkinson's disease: A systematic literature review of preclinical studies. *Brain Sciences*, *11*(12), 1573. https://doi.org/10.3390/brainsci11121573

[12] Patel, P., & Curry, S. (2026). *Cannabidiol (CBD) in clinical care*. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK556048/

[13] Safi, K., Sobieraj, J., Błaszkiewicz, M., Żyła, J., Salata, B., & Dzierżanowski, T. (2024). Tetrahydrocannabinol and cannabidiol for pain treatment—An update on the

evidence. *Biomedicines*, *12*(2), 307. https://doi.org/10.3390/biomedicines12020307

[14] Hickey, J. (2024). *Elucidating the cytoprotective effects of the phytocannabinoids, cannabidiol and delta-9-tetrahydrocannabinol, and the role of epigenetics in models of Alzheimer's disease*. Doctoral Dissertation, University of Guelph.

[15] Haghdoost, M., DePorre, Y., Figi, M., Young, S., Krebs, C., & Bonn-Miller, M. O. (2025). An unexpected activity of a minor cannabinoid: Cannabicyclol (CBL) is a potent positive allosteric modulator of serotonin 5-ht1a receptor. *Journal of Natural Products*, *88*(1), 58–66. https://doi.org/10.1021/acs.jnatprod.4c00977

[16] Bukowska, B. (2024). Current and potential use of biologically active compounds derived from *Cannabis sativa L*. In the treatment of selected diseases. *International Journal of Molecular Sciences*, *25*(23), 12738. https://doi.org/10.3390/ijms252312738

[17] Lourenço, D. M. (2023). *Uncovering the neurogenic potential of cannabinoids upon adult neural stem modulation: Cannabidivarin as a novel modulator of adult neurogenesis*.

[18] Lowe, H., Toyang, N., Steele, B., Bryant, J., & Ngwa, W. (2021). The endocannabinoid system: A potential target for the treatment of various diseases. *International Journal of Molecular Sciences*, *22*(17), 9472. https://doi.org/10.3390/ijms22179472

[19] Bonn-Miller, M. O., Feldner, M. T., Bynion, T. M., Eglit, G. M., Brunstetter, M., Kalaba, M., . . . , & Hennesy, M. (2024). A double-blind, randomized, placebo-controlled study of the safety and effects of CBN with and without CBD on sleep quality. *Experimental and Clinical Psychopharmacology*, *32*(3), 277–284. https://doi.org/10.1037/pha0000682

[20] Nachnani, R., Raup-Konsavage, W. M., & Vrana, K. E. (2021). The pharmacological case for cannabigerol. *The Journal of Pharmacology and Experimental Therapeutics*, *376*(2), 204–212. https://doi.org/10.1124/jpet.120.000340

[21] Calapai, F., Cardia, L., Esposito, E., Ammendolia, I., Mondello, C., Lo Giudice, R., . . . , & Mannucci, C. (2022). Pharmacological aspects and biological effects of cannabigerol and its synthetic derivatives. *Evidence-Based Complementary and Alternative Medicine*, *2022*, 1–14. https://doi.org/10.1155/2022/3336516

[22] Latif, S., Jahangeer, M., Razia, D. M., Ashiq, M., Ghaffar, A., Akram, M., . . . , & Ansari, M. A. (2021). Dopamine in Parkinson's disease. *Clinica Chimica Acta*, *522*, 114–26. https://doi.org/10.1016/j.cca.2021.08.009

[23] Ramesh, S., & Arachchige, A. S. P. M. (2023). Depletion of dopamine in Parkinson's disease and relevant therapeutic options: A review of the literature. *AIMS Neuroscience*, *10*(3), 200. https://doi.org/10.3934/Neuroscience.2023017

[24] Dong-Chen, X., Yong, C., Yang, X., Chen-Yu, S., & Li-Hua, P. (2023). Signaling pathways in Parkinson's disease: Molecular mechanisms and therapeutic interventions. *Signal Transduction and Targeted Therapy*, *8*(1), 73. https://doi.org/10.1038/s41392-023-01353-3

[25] Özdemir, Z., Alagöz, M. A., Bahçecioğlu, Ö. F., & Gök, S. (2021). Monoamine oxidase-B (MAO-B) inhibitors in the treatment of alzheimer's and parkinson's disease. *Current Medicinal Chemistry*, *28*(29), 6045–6065. https://doi.org/10.2174/0929867328666210203204710

[26] Oyovwi, M. O., Udi, O. A., Atere, A. D., Joseph, G. U., & Ogbutor, U. G. (2025). Molecular pathways: The quest for effective MAO-B inhibitors in neurodegenerative therapy. *Molecular Biology Reports*, *52*(1), 240. https://doi.org/10.1007/s11033-025-10349-x

[27] Masood, N., & Jimenez-Shahed, J. (2023). Effective management of "OFF" episodes in Parkinson's disease: Emerging treatment strategies and unmet clinical needs. *Neuropsychiatric Disease and Treatment*, *19*, 247–266. https://doi.org/10.2147/NDT.S273121

[28] Sivanandy, P., Leey, T. C., Xiang, T. C., Ling, T. C., Han, Wey., A, S., . . . , & Semilan, S. L. A. (2021). Systematic review on parkinson's disease medications, emphasizing on three recently approved drugs to control parkinson's symptoms. *International Journal of Environmental Research and Public Health*, *19*(1), 364. https://doi.org/10.3390/ijerph19010364

[29] Chew, Z. X., Lim, C. L., Ng, K. Y., Chye, S. M., Ling, A. P. K., & Koh, R. Y. (2023). The role of monoamine oxidase B inhibitors in the treatment of parkinson's disease—An update. *CNS & Neurological Disorders—Drug Targets*, *22*(3), 329–352. https://doi.org/10.2174/1871527321666211231100255

[30] Mori, A., Chen, J.-F., Uchida, S., Durlach, C., King, S. M., & Jenner, P. (2022). The pharmacological potential of adenosine A2A receptor antagonists for treating parkinson's disease. *Molecules*, *27*(7), 2366. https://doi.org/10.3390/molecules27072366

[31] Morash, M. G., Nixon, J., Shimoda, L. M. N., Turner, H., Stokes, A. J., Small-Howard, A. L., & Ellis, L. D. (2022). Identification of minimum essential therapeutic mixtures from cannabis plant extracts by screening in cell and animal models of Parkinson's disease. *Frontiers in Pharmacology*, *13*, 907579. https://doi.org/10.3389/fphar.2022.907579

[32] Segura-Aguilar, J., & Paris, I. (2022). Mechanisms of dopamine oxidation and parkinson's disease. In R. M. Kostrzewa (Ed.), *Handbook of Neurotoxicity* (pp. 1–36). Springer International Publishing. https://doi.org/10.1007/978-3-030-71519-916-1

[33] Singh, A., Sinha, S., & Singh, N. K. (2024). Dietary natural flavonoids: Intervention for MAO-B against Parkinson's disease. *Chemical Biology & Drug Design*, *104*(3), e14619. https://doi.org/10.1111/cbdd.14619

[34] Mateev, E., Georgieva, M., Mateeva, A., Zlatkov, A., Ahmad, S., Raza, K., . . . , & Barh, D. (2023). Structure-based design of novel MAO-B inhibitors: A review. *Molecules*, *28*(12), 4814. https://doi.org/10.3390/molecules28124814

[35] Gaweska, H., & Fitzpatrick, P. F. (2011). Structures and mechanism of the monoamine oxidase family. *Biomolecular Concepts*, *2*(5), 365. https://doi.org/10.1515/BMC.2011.030

[36] Kaur, G., Goyal, D., & Goyal, B. (2023). Computational modeling of MAO inhibitors as anti-Alzheimer agents. In K. Roy (Ed.), *Computational Modeling of Drugs Against Alzheimer's Disease* (pp. 325–353). Springer US. https://doi.org/10.1007/978-1-0716-3311-3_11

[37] Azam, F., Abodabos, H. S., Taban, I. M., Rfieda, A. R., Mahmood, D., Anwar, M. J., ..., & Ali, H. I. (2019). Rutin as promising drug for the treatment of Parkinson's disease: An assessment of MAO-B inhibitory potential by docking, molecular dynamics and DFT studies. *Molecular Simulation*, *45*(18), 1563–1571. https://doi.org/10.1080/08927022.2019.1662003

[38] Rachel Thomas, R., Chandran, N., Thomas Parambi, D. G., Kumar, S., Alsahli, T. G., Verma, S., . . . , & Mathew, B. (2024). A comprehensive review of the molecular dynamic study of chalcones, coumarins and chromones as selective

MAO-B Inhibitors [2015-Till Date]. *ChemistrySelect*, *9*(27), e202401709. https://doi.org/10.1002/slct.202401709

[39] Kumar, G., Mishra, S., Seboletswe, P., Manhas, N., Ghumran, S., Roquet-Banères, F., . . . , & Singh, P. (2025). Isoniazid–rhodanine molecular hybrids: Design, synthesis, antimycobacterial activity and computational validation. *RSC Advances*, *15*(38), 31272–31288. https://doi.org/10.1039/d5ra03641k

[40] El Fatimi, H., Khalki, H., Loughzail, M., Hachimi, N., Elaazri, H., Baouid, A., . . . , & Khalki, L. (2026). In vivo and in silico toxicity profiling of a novel 1,5-benzodiazepine derivative. *Drug and Chemical Toxicology*, *49*(2), 326–343. https://doi.org/10.1080/01480545.2025.2606105

[41] Filimonov, D. A., Lagunin, A. A., Gloriozova, T. A., Rudik, A. V., Druzhilovskii, D. S., Pogodin, P. V., & Poroikov, V. V. (2014). Prediction of the biological activity spectra of organic compounds using the pass online web resource. *Chemistry of Heterocyclic Compounds*, *50*(3), 444–457. https://doi.org/10.1007/s10593-014-1496-1

[42] Jost, W. H. (2022). A critical appraisal of MAO-B inhibitors in the treatment of Parkinson's disease. *Journal of Neural Transmission*, *129*(5–6), 723–736. https://doi.org/10.1007/s00702-022-02465-w

[43] Ribeiro, L. V., Massuda, L. E., Gontijo, V. S., & Viegas, C. (2025). Monoamine oxidase inhibitors in drug discovery against parkinson's disease: An update. *Pharmaceuticals*, *18*(10), 1526. https://doi.org/10.3390/ph18101526

[44] Solis-Vasquez, L., Tillack, A. F., Santos-Martins, D., Koch, A., LeGrand, S., & Forli, S. (2022). Benchmarking the performance of irregular computations in AutoDock-GPU molecular docking. *Parallel Computing*, *109*, 102861. https://doi.org/10.1016/j.parco.2021.102861

[45] Azam, S. E., Loureiro, L., Vicente, A. A., & Vardanega, R. (2026). Chemical composition, classification, and metabolism of cannabinoids. In S. E. Azam, L. Loureiro, A. A. Vicente, & R. Vardanega (Eds.), *Cannabinoids in Food Science* (pp. 9–33). Springer Nature Switzerland. https://doi.org/10.1007/978-3-032-11546-1_2

[46] Nigro, E., Formato, M., Crescente, G., & Daniele, A. (2021). Cancer initiation, progression and resistance: Are phytocannabinoids from *Cannabis sativa L*. Promising compounds? *Molecules*, *26*(9), 2668. https://doi.org/10.3390/molecules26092668

[47] Poças, C. S. (2017). Canabinóides: Perspetivas no tratamento da doença de parkinson. *Master's Thesis, Universidade de Coimbra (Portugal)*.

[48] Itturriet, A. N. S., Dias, R. S., & Kremer, F. S. (2025). In silico screening of anti-Parkinsonian multi-target drugs from natural compounds. *Biotechnology Research and Innovation Journal*, *9*(1), e2025024. https://doi.org/10.4322/biori.00152024

[49] Lu, H.-C., & Mackie, K. (2021). Review of the endocannabinoid system. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *6*(6), 607–615. https://doi.org/10.1016/j.bpsc.2020.07.016

[50] Kibret, B. G., Canseco-Alba, A., Onaivi, E. S., & Engidawork, E. (2023). Crosstalk between the endocannabinoid and mid-brain dopaminergic systems: Implication in dopamine dysregulation. *Frontiers in Behavioral Neuroscience*, *17*, 1137957. https://doi.org/10.3389/fnbeh.2023.1137957

[51] Bhattacharya, P., Chatterjee, S., & Roy, D. (2023). Impact of exercise on brain neurochemicals: A comprehensive review. *Sport Sciences for Health*, *19*(2), 405–452. https://doi.org/10.1007/s11332-022-01030-y

[52] Wang, L., Wu, X., Yang, G., Hu, N., Zhao, Z., Zhao, L., & Li, S. (2022). Cannabidiol alleviates the damage to dopaminergic neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinson's disease mice via regulating neuronal apoptosis and neuroinflammation. *Neuroscience*, *498*, 64–72. https://doi.org/10.1016/j.neuroscience.2022.06.036

[53] Mancini, M., Calculli, A., Di Martino, D., & Pisani, A. (2024). Interplay between endocannabinoids and dopamine in the basal ganglia: Implications for pain in Parkinson's disease. *Journal of Anesthesia, Analgesia and Critical Care*, *4*(1), 33. https://doi.org/10.1186/s44158-024-00169-z

[54] Holst, B., & Williamson, G. (2008). Nutrients and phytochemicals: From bioavailability to bioefficacy beyond antioxidants. *Current Opinion in Biotechnology*, *19*(2), 73–82. https://doi.org/10.1016/j.copbio.2008.03.003

[55] Alexander, S. P. H., & Randall, M. (2007). Cannabinoids and their actions. *British Journal of Pharmacology*, *152*(5), 557–558. https://doi.org/10.1038/sj.bjp.0707483

[56] Gray, R., Patel, S., Ives, N., Rick, C., Woolley, R., Muzerengi, S., . . . , & Clarke, C. E. (2022). Long-term effectiveness of adjuvant treatment with catechol-o-methyltransferase or monoamine oxidase B inhibitors compared with dopamine agonists among patients with parkinson disease uncontrolled by levodopa therapy: The PD MED randomized clinical trial. *JAMA Neurology*, *79*(2), 131. https://doi.org/10.1001/jamaneurol.2021.4736

[57] Saini, N., Singh, N., Kaur, N., Garg, S., Kaur, M., Kumar, A., . . . , & Sohal, H. S. (2024). Motor and non-motor symptoms, drugs, and their mode of action in Parkinson's disease (PD): A review. *Medicinal Chemistry Research*, *33*(4), 580–599. https://doi.org/10.1007/s00044-024-03203-5

[58] Di Biase, L., Pecoraro, P. M., Carbone, S. P., Caminiti, M. L., & Di Lazzaro, V. (2023). Levodopa-induced dyskinesias in parkinson's disease: An overview on pathophysiology, clinical manifestations, therapy management strategies and future directions. *Journal of Clinical Medicine*, *12*(13), 4427. https://doi.org/10.3390/jcm12134427

[59] Pacureanu, L., Bora, A., & Crisan, L. (2023). New insights on the activity and selectivity of MAO-B inhibitors through in silico methods. *International Journal of Molecular Sciences*, *24*(11), 9583. https://doi.org/10.3390/ijms24119583

[60] Hassanzadeh, K., Buccarello, L., Dragotto, J., Mohammadi, A., Corbo, M., & Feligioni, M. (2020). Obstacles against the marketing of curcumin as a drug. *International Journal of Molecular Sciences*, *21*(18), 6619. https://doi.org/10.3390/ijms21186619

[61] Khan, A., Ansari, M. S., Khan, A. A., Abbas, K., & Alam, M. (2026). Therapeutic evaluation of phytochemicals present in Nigella sativa seed oil for anxiolytic activity against the GABA-B receptor: A gas chromatography-mass spectrometry (GC–MS)-supported molecular dynamics-based in silico study. *In Silico Pharmacology*, *14*(1), 114. https://doi.org/10.1007/s40203-026-00612-9

[62] Liu, Z. H., Wang, J. L., Zhao, Y. N., Li, J., Shi, Z. C., Wang, D., …, & Zhang, S. J. (2023). A new dihydrostilbene from aerial part of *Cannabis sativa*. *Zhongguo Zhong yao zazhi = Zhongguo Zhongyao Zazhi = China Journal of Chinese Materia Medica*, *48*(4), 985–992. https://doi.org/10.19540/j.cnki.cjcmm.20220406.201

[63] Tuli, H. S., Sandhu, S. S., & Sharma, A. K. (2014). Pharmacological and therapeutic potential of Cordyceps with special reference to Cordycepin. *3 Biotech*, *4*(1), 1–12. https://doi.org/10.1007/s13205-013-0121-9

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