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Molecular Docking Analysis of Phytochemicals in Ethanolic Extract of Thalictrum foliolosum in Parkinson's Disease

Nagaraj N Durgadasheemi[1], Rakesh Kumar Jat[2*], Nagesh D R[3]

[1]Research Scholar, Institute of Pharmacy, Shri JJT University, Vidyanagari, Jhunjhunu Churu Road, Chudela, District - Jhunjhunu Rajasthan
[2]Professor and Principal, Institute of Pharmacy, Shri JJT University, Vidyanagari, Jhunjhunu Churu Road, Chudela, District - Jhunjhunu Rajasthan
[3]Professor, East point college of Pharmacy, Department of Pharmaceutics, Bidarahalli, Virgo Nagar post, Bangalore
Email: rakeshjat75@yahoo.co.in

Parkinson's disease (PD) is a neurodegenerative condition that is distinguished by dopaminergic neuron loss in the substantia nigra pars compacta and the presence of Lewy bodies. Current pharmacological treatments frequently result in side effects and limited efficacy, necessitating alternative therapeutic techniques. This study looks into the possibility of phytochemicals from Thalictrum foliolosum, a Himalayan medicinal plant, to act as dopamine D3 receptor inhibitors and reduce Parkinson's disease symptoms. T. foliolosum ethanolic extracts were tested for active phytochemicals using liquid chromatography-mass spectrometry (LC-MS). Molecular docking studies were carried out against the crystal structure of the dopamine D3 receptor (PDB ID: 3PBL) to determine binding affinities and interactions. Jatrorrhizine had the highest docking score (-8.8 kcal/mol), followed by berberine and rutin (-8.6 kcal/mol each), indicating a robust receptor binding. The docking studies revealed that Jatrorrhizine has the closest docking score (-8.8 kcal/mol) to that of the standard Levodopa (-9.1 kcal/mol), proving that it has the best molecular docking result for the dopamine D3 receptor. This work underscores the value of T. foliolosum as a source of bioactive compounds for PD management and provides a foundation for further in vitro and in vivo investigations.

Keywords: Parkinson Disease, Levodopa, D3 receptor, Thalictrum foliolosum, Substantia nigra pars compacta, etc.

1. Introduction

Thalictrum is a member of Ranunculaceae's Thalictroideae subfamily, which includes the genera Aquilegia, Dichocarpum, Enemion, Isopyrum, Leptopyrum, Paraquilegia, Paropyrum, Semiaquilegia, Thalictrum, and Urophysa [1,2]. Thalictrum contains 200 species that are found in Asia, Europe, Africa, North America, and South America. Thalictrum foliolosum DC

is extensively distributed plant in the Himalayan region spanning India, Nepal, Bhutan, South East Tibet and Burma between an altitude range of 1000–3400 m [3,4]. Within India, it was reported in Jammu and Kashmir, Himachal Pradesh, Punjab, Uttar Pradesh, Delhi, Sikkim, Arunachal Pradesh, Meghalaya, Bihar, Orissa, Andhra Pradesh, and Tamil Nadu [4,5]. In Himachal Pradesh, it is distributed in various regions such as Chamba, Kangra, Kinnaur, Kullu, Mandi, Lahaul-Spiti, Solan, Shimla and Sirmour districts up to an elevation of 3000 m [6,7].

The root of this plant is traditionally used as a tonic, antiperiodic, diuretic, febrifuge, purgative, and stomachic. They are used to treat atonic dyspepsia, edema, skin conditions, flatulence, jaundice, and visceral blockages [8]. It heals corneal ulcers and night blindness. The herb has been used to treat oriental sores, diarrhea, trachoma, diabetes type 2, hypercholesterolemia, and congestive cardiac failure [9,10]. The ethnic tribes of East Godavari District employ a root concoction to treat stomach-ache. Locals in Himachal Pradesh, India, utilize the plant paste to treat skin problems and snake bites. The juice from the leaves is administered to boils and acne. The root has diuretic, ophthalmic, and purgative properties, as well as a stomach-ache salve. It is used as a tonic for dyspepsia and to treat indigestion, fever, and toothaches [11]. The Naga tribes in Manipur, India, use the rhizome to treat fever, piles, dyspepsia, jaundice, and diarrhea. The Adi and Monpa tribes of Arunachal Pradesh utilize the plant to treat malaria and gastrointestinal issues [12].

Neurodegenerative diseases are a class of illnesses that cannot be controlled and have a negative impact on a person's health. This category includes disorders such as Alzheimer's, Parkinson's, Huntington's, spinal and bulbar muscular atrophy, spinocerebellar ataxia, and amyotrophic lateral sclerosis [13]. One of the most prevalent neurodegenerative diseases with an unpredictable dynamic pathology is Parkinson's disease (PD). Dr. James Parkinson initially referred to Parkinson's disease as "shaking palsy" in 1817. The prevalence of Parkinson's disease (PD) is approximately 2% in those over 60 and 4% in people over 80. Parkinson's disease (PD) is a progressive neurological illness that varies with age. The substantia nigra pars compacta (SNpc) dopaminergic neurons that project to the striatum is selectively lost, and Lewy bodies-intracytoplasmic inclusions containing ubiquitin and α-synuclein are present [14]. Typical symptoms include hand tremors, postural instability, muscle rigidity, and voluntary motor imbalance that slows and makes it difficult to start motions. At the molecular level, PD is linked to mitochondrial dysfunction brought on by extreme oxidative stress. The suppression of mitochondrial complex-I appears to be particularly important. Genetic factors and exposure to environmental pollutants are likely involved in the etiology of Parkinson's disease [15].

Levodopa with a DOPA decarboxylase inhibitor have been the first-line and gold standard combo for decades. Other medication types, such selegiline, benztropine, and orphenadrine, work by reversing the symptoms of Parkinson's disease. However, a wide range of adverse effects, including nausea, vomiting, respiratory problems, hallucinations, mania, dyskinesia, convulsions, and anxiety, are often associated with long-term therapy with these medications [16]. Because traditional cures are less expensive and have fewer adverse effects, their demand has been rising.

D3 Receptor is one of the dopamine receptor subtypes primarily involved in modulating

dopamine signaling in the brain. Overactivation of D3 receptors in certain brain regions (such as the basal ganglia) can contribute to motor and behavioral dysfunction in Parkinson's disease [17,18]. By inhibiting dopamine D3 receptors on the presynaptic neurons can increase dopamine availability in the midbrain, including the substantia nigra pars compacta (SNpc). Therefore, the goal of the current study was to determine how T. foliolosum inhibits the Dopamine D3 receptor to prevent Parkinson's disease. This work was conducted by first utilizing LCMS to identify the phytochemicals present in the ethanolic crude extract, and then using docking against the crystal structure of the Dopamine D3 receptor to analyze the phytochemicals mechanism of action.

2. MATERIAL AND METHODS:

Plant material collection:

The leaves of Thallictrum foliolosum were collected in January 2024 from the outskirt area of Mandi, Himachal Pradesh. The plant was authenticated by Himachal Pradesh State Biodiversity Board, Shimla, Himachal Pradesh. The leaves were shade-dried at room temperature, and powdered with mortar and pestle kept in an amber colour container prior to analysis.

Preparation of the crude extract:

The plant leaves were first cleaned with water to get rid of dirt and other foreign objects, then they were separated and allowed to dry in the shade. After being ground into a coarse powder, the dried leaves were run through screen No. 14. The 20 g of dried powdered T. foliolosum leaves that were collected were put in a thimble-shaped tube of the Soxhlet apparatus and extracted with 300 mL of ethanol at 60–65 °C for three to four hours. The final dried extract samples were stored in the refrigerator at a low temperature for additional research after the produced ethanolic extract was filtered while still hot and dried by evaporation using a rotating vacuum evaporator. For additional examination, the residue from each extract was dissolved in the same solvent.

LC-MS Analysis:

The polyphenols in an ethanolic extract of leaves were measured using chromatography, as previously reported [19]. The chromatographic system comprises of an Agilent 1100 series HPLC instrument (Santa Clara, USA) with an MS detector. Analytical separation was performed using a C18 column (4.6 mm × 100 mm × 5 μm, Agilent Technology) with a flow rate of 0.8/min and two mobile solvent phases (eluent A = 10 mM ammonium acetate and 1% acetic acid in water; eluent B = 1% acetic acid in methanol). The gradient elution was carried out as follows: 0.3 minute, 15-50% A; 3-5.5 minutes, 50-90% A; 5.5-9 minutes, 90% A; 9-9.5 minutes, 90-15% A; and 9.5-10 minutes, 15% A. The sample injection volume was 20 μL, and the column temperature was fixed at 40 °C. The retention durations and mass spectra of the compounds were compared to those of already known compounds in the NIST library. The reported data includes the compound, name, retention time, and concentration. The structures, molecular weight, and pubchem ID were derived from the PubChem database.

Molecular docking studies:

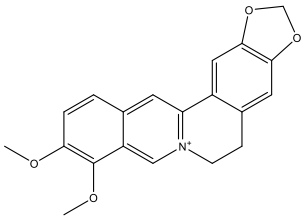
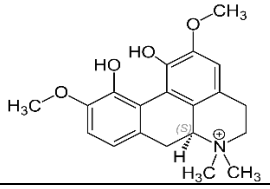
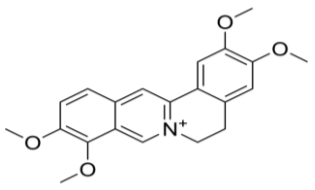
To investigate the interactions between phytochemicals from Thalictrum foliolosum and the standard drug Levodopa with molecular targets, the crystal structure of the human dopamine D3 receptor (PDB ID: 3PBL) (https://www.rcsb.org/structure/3pbl) was obtained from the RCSB Protein Data Bank [20] Several preparatory steps were performed on the retrieved crystal structure before molecular docking. These steps included removing water molecules and ions and adding nonpolar hydrogens. The protein was then minimized and optimized using AutoDock Tool v1.5.7 (https://autodocksuite.scripps.edu/adt) [21]. Following energy minimization, the structures of Levodopa and the phytochemicals were converted to pdbqt format using PyRx. Molecular docking was subsequently conducted using the PyRx virtual screening tool (https://sourceforge.net/projects/pyrx) [22]

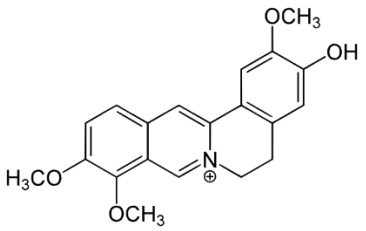
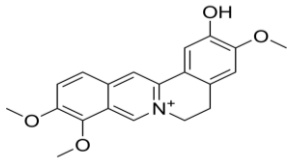
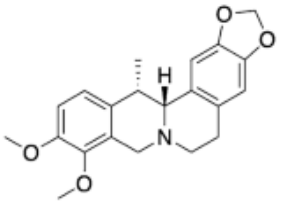
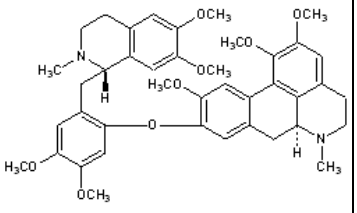
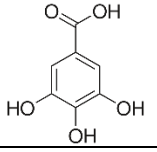
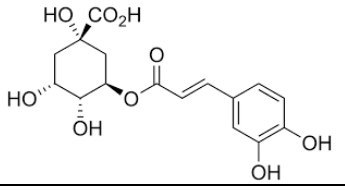
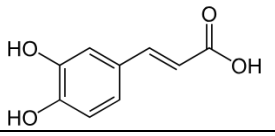
3. RESULTS AND DISCUSSION:

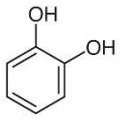
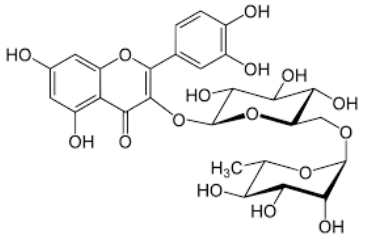
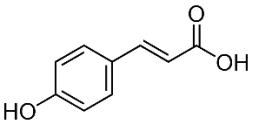
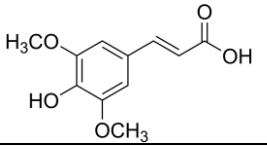
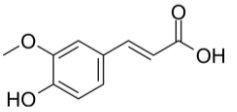
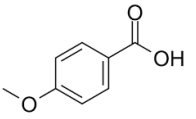
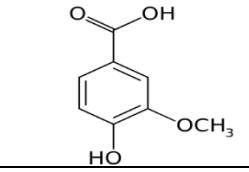
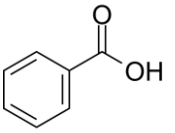
LCMS analysis:

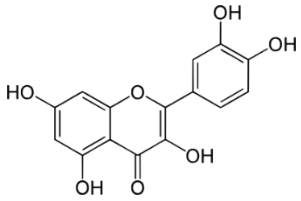
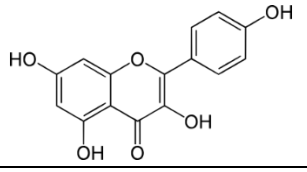
Total 20 compounds were identified from ethe ethanolic extract of the T. foliolosum leaves extract. Compounds names, molecular formula, molecular weight, retention time and their chemical structure of identified compounds tabulated in table 1.

Table 1. Bioactive compounds present in the ethanolic extract of T. foliolosum leaves

Compound Name	Molecular Formula	Molecular Weight (g/mol)	Retention Time (min)	Chemical Structure
Berberine	$C_{20}H_{18}NO_4$	336.37	15.2	 Berberine
Magnoflorine	$C_{20}H_{24}NO_4$	342.41	12.4	
Palmatine	$C_{21}H_{22}NO_4$	352.41	14.8	

Jatrorrhizine	$C_{20}H_{20}NO_4$	338.38	13.7	
Columbamine	$C_{20}H_{20}NO_4$	339.39	16.5	
Thalictricavine	$C_{21}H_{23}NO_4$	608.73	18.0	
Thalicarpine	$C_{41}H_{48}N_2O_8$	696.8		
Gallic Acid	$C_7H_6O_5$	170.12	5.2 - 6.5	
Chlorogenic Acid	$C_{16}H_{18}O_9$	354.31	9.0 - 10.5	
Caffeic Acid	$C_9H_8O_4$	180.16	8.5 - 9.5	

Catechol	$C_6H_6O_2$	110.11	4.0 - 5.0	
Rutin	$C_{27}H_{30}O_{16}$	610.52	18.0 - 19.5	
p-Coumaric Acid	$C_9H_8O_3$	164.16	12.0 - 13.0	
Sinapic Acid	$C_{11}H_{12}O_5$	224.21	14.0 - 15.0	
Ferulic Acid	$C_{10}H_{10}O_4$	194.18	12.0 - 13.5	
Anisic Acid	$C_8H_8O_3$	152.15	8.0 - 9.0	
Vanillic Acid	$C_8H_8O_4$	168.15	10.5 - 11.5	
Benzoic Acid	$C_7H_6O_2$	122.12	7.0 - 8.0	

Quercetin	$C_{15}H_{10}O_7$	302.24	17.0 - 18.5	
Kaempferol	$C_{15}H_{10}O_6$	286.24	16.0 - 17.5	

Molecular docking analysis:

The molecular docking analysis of Jatrorrhizine with the human dopamine D3 receptor (PDB ID: 3PBL) reveals a range of non-covalent interactions that suggest a favorable and stable binding conformation, supported by a docking score of -8.8 kcal/mol. (Table 2) shows the details of docking scores for phytochemicals from Thalictrum foliolosum. This score indicates a strong binding affinity, with the negative value reflecting the energetically favorable nature of the interaction. The ligand engages in numerous van der Waals interactions with residues such as Cys181, Phe106, Thr369, Val86, Asp110, Trp342, Phe346, Ser196, Phe188, Phe345, His349, and Ser182. These interactions suggest that Jatrorrhizine fits well within the hydrophobic regions of the receptor, contributing to the overall binding stability. Additionally, a conventional hydrogen bond with Ser192 highlights the specificity of the interaction, likely anchoring the ligand within the binding pocket and aiding its orientation for effective binding. Further stabilization is provided by a carbon-hydrogen bond with Thr373, which, although weaker, adds to the overall interaction profile. Aromatic interactions are also significant, with a pi-sigma interaction involving Val111 and a pi-pi T-shaped interaction with Tyr365, which facilitate tight binding through complementary stacking and alignment of aromatic rings. Hydrophobic contacts are reinforced by an alkyl interaction with Leu89, and a pi-sulfur interaction with Cys114, underscoring the importance of electronic and hydrophobic interactions in stabilizing the ligand. The diversity and number of these interactions suggest that Jatrorrhizine has a strong affinity for the D3 receptor, potentially indicating its ability to modulate receptor activity. (Figure 1) illustrates Jatrorrhizine's interactions with the dopamine receptor, showing 2D contacts, and comparison with levodopa.

Table 2. Phytochemicals from Thalictrum Foliolosum and the standard drug Levodopa demonstrating docking scores with the dopamine D3 receptor (PDB ID: 3PBL).

S. No	Phytochemical Name	Docking Score (kcal/mol)
1	Jatrorrhizine	-8.8
2	Berberine	-8.6
3	Rutin	-8.6
4	Columbamine	-7.9
5	Palmatine	-7.8

6	Magnoflorine	-7.7
7	Thalicarpine	-7.6
8	Quercetin	-7.4
9	Thalictricavine	-7.4
10	Kaempferol	-7.3
11	Chlorogenic Acid	-7.2
12	Ferulic Acid	-6.5
13	Sinapic Acid	-6.3
14	p-Coumaric Acid	-6.2
15	Caffeic Acid	-6
16	Gallic Acid	-6
17	Vanillic Acid	-6
18	Anisic Acid	-5.3
19	Benzoic Acid	-5.2
20	Catechol	-4.5
21	Levodopa	-9.2

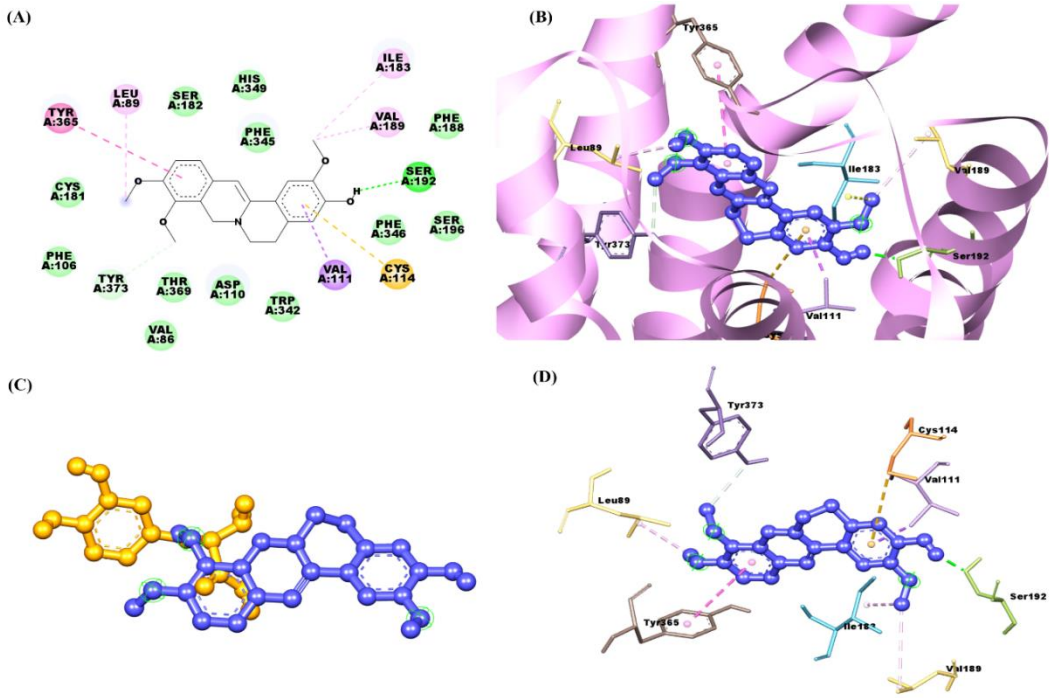


Figure 1. shows the docking interactions of Jatrorrhizine with the dopamine D3 receptor (PDB ID: 3PBL). (A) displays a 2D interaction map highlighting key receptor contacts. (B) presents a 3D view of Jatrorrhizine's binding, focusing on hydrogen bonds and hydrophobic interactions. (C) overlays Jatrorrhizine (blue) with levodopa (orange), showing similar

binding patterns. (D) provides a close-up of key stabilizing interactions. Together, these visuals compare the binding of Jatrorrhizine and levodopa within the receptor.

The molecular docking analysis of Thalictrum foliolosum phytochemicals revealed significant inhibitory activity against the dopamine D3 receptor, a critical target in Parkinson's disease management. Jatrorrhizine exhibited the strongest binding affinity, suggesting its potential as a lead compound. The interactions observed, such as hydrogen bonding and hydrophobic contacts, contribute to the compound's stability and specificity in receptor binding. Compared to levodopa, a standard treatment for PD, the phytochemicals demonstrated comparable docking scores, indicating their therapeutic relevance. This study emphasizes the importance of exploring traditional medicinal plants for neurodegenerative disease therapies, given their lower side effect profiles and cost-effectiveness. While the findings are promising, the transition from molecular docking to clinical application requires extensive in vitro and in vivo studies to confirm efficacy and safety. Future work should also investigate the synergistic effects of these compounds and their bioavailability in biological systems.

4. CONCLUSION:

The present study highlights the therapeutic potential of phytochemicals from Thalictrum foliolosum in managing Parkinson's disease. Through LC-MS analysis and molecular docking, key bioactive compounds such as jatrorrhizine, berberine, and rutin were identified as potent inhibitors of the dopamine D3 receptor, demonstrating strong binding affinities. These findings support the hypothesis that T. foliolosum phytochemicals can modulate receptor activity, potentially mitigating PD symptoms. The diverse non-covalent interactions, including hydrogen bonds and hydrophobic contacts, observed in molecular docking analyses suggest a stable and specific binding of these compounds to the receptor. This study not only reinforces the importance of traditional medicinal plants in neurodegenerative disease research but also provides a pathway for the development of plant-derived therapeutics with minimal side effects. Future research should include in vitro and in vivo evaluations to validate these findings and explore the pharmacokinetics and safety profiles of the identified compounds.

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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