XXXII SYMPOSIUM ON BIOINFORMATICS AND COMPUTER-AIDED DRUG DISCOVERY

BCADD-2026 • INTERNATIONAL ORAL PRESENTATION

ELUCIDATING THE MOLECULAR CROSSTALK BETWEEN PARKINSON'S DISEASE AND LEVODOPA-INDUCED DYSKINESIA: A NETWORK PHARMACOLOGY APPROACH

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19–21 October 2026 • Virtual • Emerging Challenges & Opportunities for In Silico Drug Discovery

Introduction

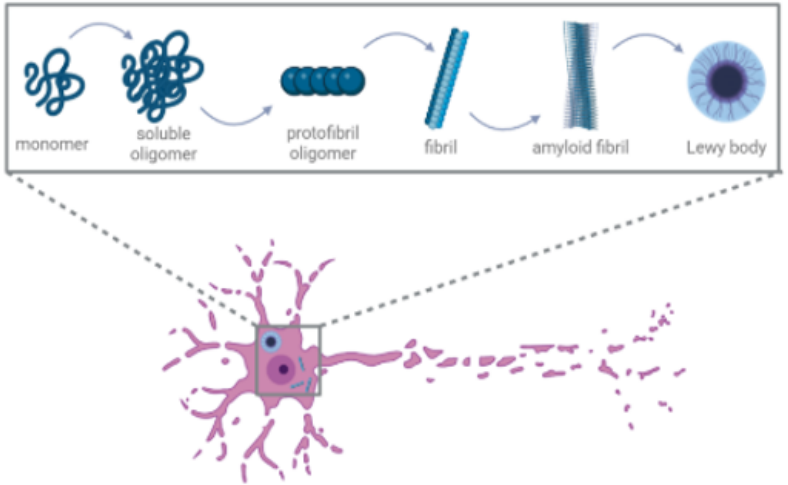
10M+ people affected by Parkinson's disease worldwide

Neuronal loss

Loss of dopaminergic neurons causes motor and non-motor symptoms (Cesaroni et al., 2022).

Pathogenesis

Involves α-synuclein, mitochondrial dysfunction and oxidative stress.



Levodopa-Induced Dyskinesia (LID)

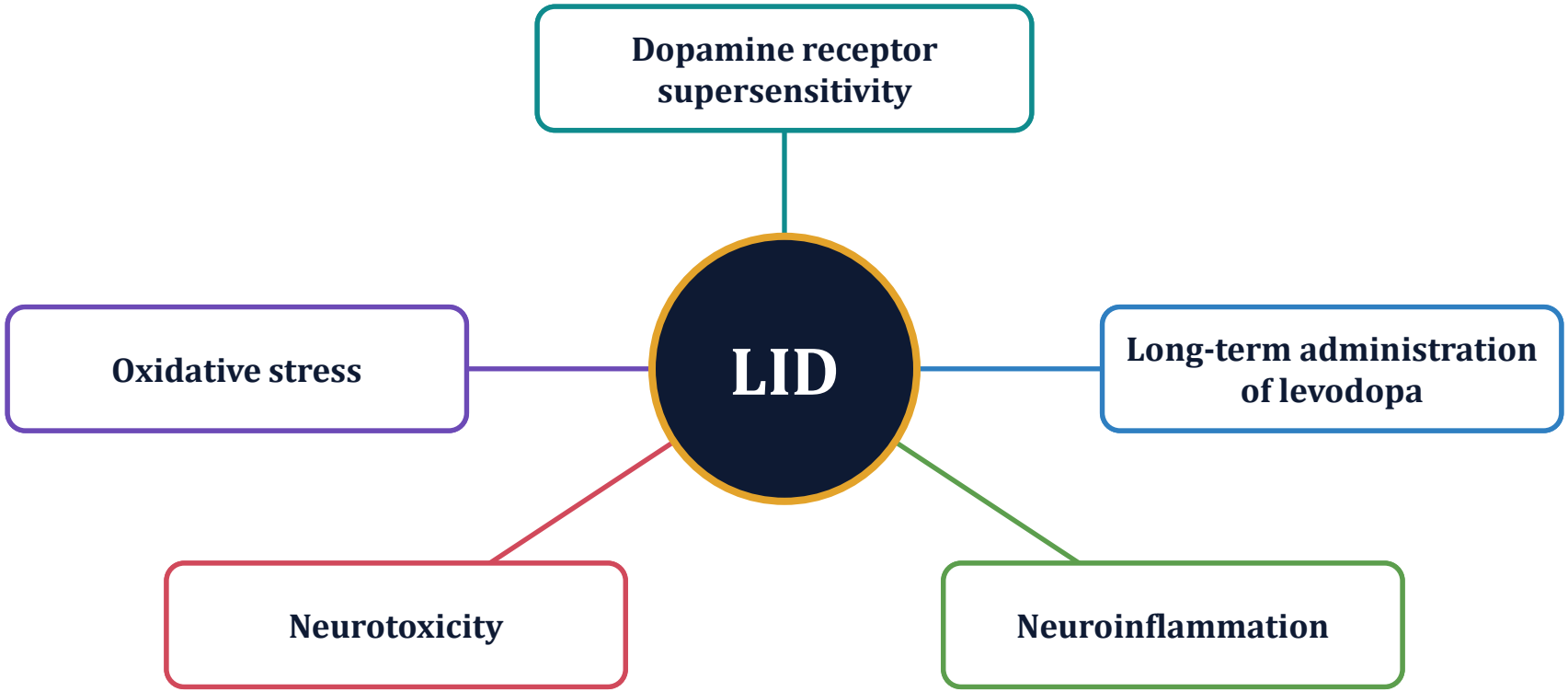
LID is characterized by abnormal involuntary movements such as choreiform movements, dystonia, facial grimacing, and repetitive jerky motions, primarily affecting the limbs, face, and trunk (Bariotto et al., 2021).


Levodopa induced Tongue Protrusion

Sequence of dopaminergic mechanisms in LID

1. **Levodopa administration**
   Introduction of levodopa to restore dopamine levels
2. **Pulsatile dopamine stimulation**
   Intermittent release causing non-physiological activity
3. **D1 receptor overactivation**
   Excessive motor excitability due to D1 receptor issues
4. **D1 receptor supersensitivity**
   Enhanced motor output and dyskinesia from D1 receptor changes
5. **D2 receptor dysfunction**
   Impaired movement inhibition due to D2 receptor dysfunction
6. **Reduced DAT activity**
   Prolonged dopamine signaling worsening dyskinesia

Pathophysiology of LID



Materials and Methods

Identification of key molecular pathways involved in PD and LID

1 Selection of databases	2 PPI network construction	3 Module detection	4 Functional enrichment analysis	5 Identification of hub genes
Retrieval of PD–LID associated genes OMIM • DisGeNET • Ensembl	**STRING database**	**MCODE**	**DAVID**	**MCC algorithm** CytoHubba in Cytoscape
Identification of shared gene set Venny	**High-confidence network validation**		**GeneCodis4**	

Phytochemical Screening via PASS

1 Download

Phytoconstituents downloaded from IMPPAT

2 Predict

Apply PASS algorithm to predict biological activity

3 Score

Probability scores generated: Pa (probability of being active) and Pi (probability of being inactive)

4 Filter

Top compounds filtered on probability threshold for the desired activity

Probability thresholds

Pa > 0.7

High potential

0.5 < Pa < 0.7

Moderate potential

Pa < 0.5

Less potential

Biological Activities Screened

Activities relevant to PD and LID disease mechanisms

1. **Anti-dyskinetic**
2. **Neuroprotective**
3. **Anti-parkinsonian**
4. **Tremor-relieving**
5. **Dopamine agonist**
6. **MAO-B inhibition**
7. **Glutamate / NMDA receptor modulation**
8. **GABAergic modulation**
9. **Anti-inflammatory**
10. **Inflammasome inhibition**

ADMET Profiling and Molecular Docking Criteria

ADMET profiling (SwissADME)

ADMET profiling and blood–brain barrier penetration

Lipinski's rule of five

BBB permeability

Oral bioavailability — **OB ≥ 30%**

Molecular docking criteria

Structure retrieval and receptor preparation

Binding energy evaluation

High affinity
ΔG ≤ −7.0 kcal/mol

Moderate affinity
ΔG between −5.0 and −7.0 kcal/mol

Results

Network pharmacology of Parkinson’s disease and levodopa-induced dyskinesia

Identification of Shared Gene Set

Parkinson's disease

2381

total genes identified

- 2295 genes unique to the condition
- Driven by neurodegenerative processes

Drug-induced dyskinesia

213

total genes identified

- 127 genes unique to the condition
- Driven by treatment-induced dyskinesia

85

shared genes

(3.4%) overlap between PD- and LID-associated genes

Overlap of PD- and LID-Associated Genes

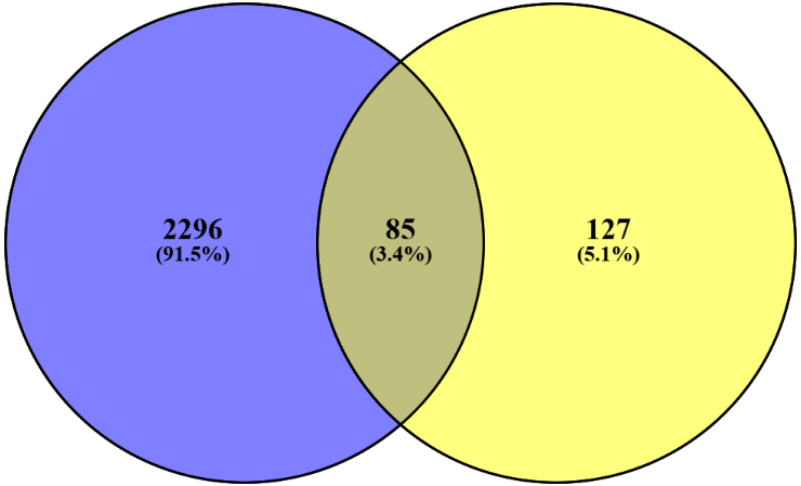
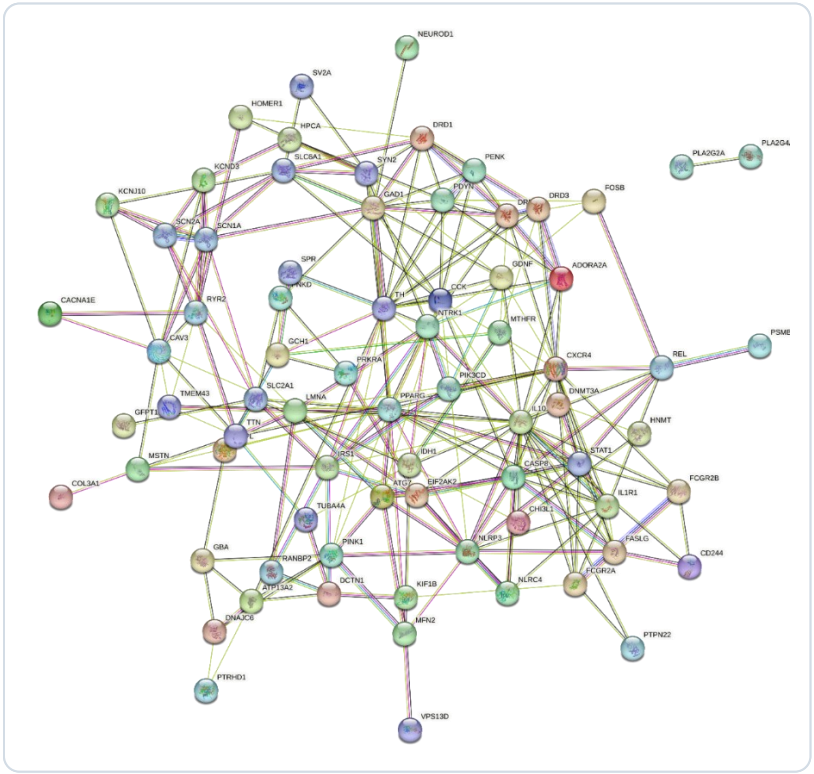


Figure 1. Venn diagram of Parkinson's disease (PD)- and levodopa-induced dyskinesia (LID)-associated genes, generated using Venny 2.1.

85 shared genes

ADORA2A, ALPL, ATG7, ATP13A2, CACNA1E, CASP8, CAT, CAV3, CCK, CD244, CHI3L1, COL3A1, CXCR4, DARS2, DCTN1, DNAJC6, DNMT3A, DRD1, DRD2, DRD3, EIF2AK2, FASLG, FCGR2A, FCGR2B, FOSB, GAD1, GBA1, GCH1, GDAP2, GDNF, GFPT1, GPR161, HNMT, HOMER1, HPCA, IDH1, IL10, IL1R1, IRS1, KCND3, KCNJ10, KIF1B, LMNA, MECR, MFN2, MPV17, MSTN, MTHFR, NEUROD1, NLRC4, NLRP3, NMNAT1, NOTCH2NLC, NTRK1, PDYN, PENK, PIK3CD, PINK1, PLA2G2A, PLA2G4A, PNKD, PPARG, PRKRA, PSMB4, PTCH2, PTPN22, PTRHD1, RANBP2, REL, RYR2, SCN1A, SCN2A, SLC2A1, SLC41A1, SLC6A1, SPR, STAT1, SV2A, SYN2, TH, TMEM43, TNR, TTN, TUBA4A, VPS13D

Protein–Protein Interaction Network



85 nodes

241 edges

5.67 average node degree

PPI enrichment p-value < 1.0×10^{-16} (medium confidence, 0.400)

Figure 2. PPI network of shared PD and LID genes constructed using STRING v11.5.

High-Confidence Network Validation

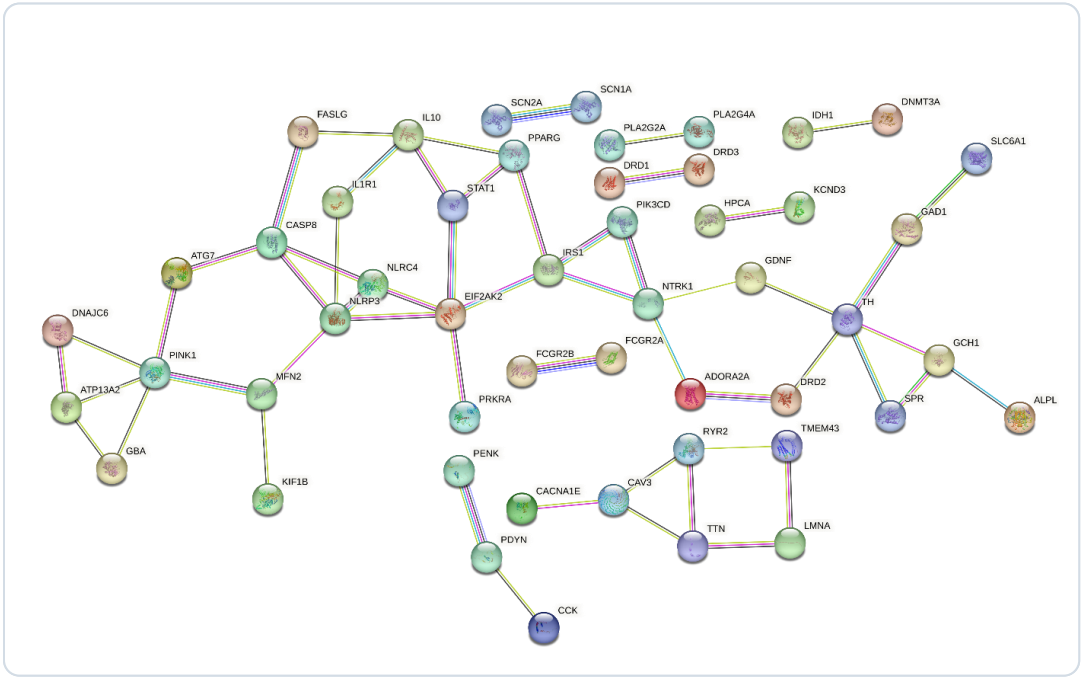


Figure 3. High-confidence PPI network of shared PD and LID genes generated using STRING v11.5 at confidence score 0.700.

55

edges

1.29

average node degree

2.75×10^{-10}

PPI enrichment p-value

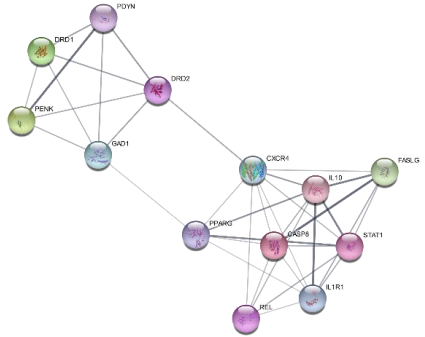
Confidence threshold 0.700

Network Topology: Medium vs High Confidence

Metric	Medium confidence (0.400)	High confidence (0.700)
Total Nodes	85	85
Total Edges	241	55
Average Node Degree	5.67	1.29
Avg. Local Clustering Coefficient	0.547	0.325
Expected Edges (Random)	126	21
PPI Enrichment p-value	$<1.0 \times 10^{-16}$	2.75×10^{-10}

Table 2. Comparison of STRING PPI network topology at medium (0.400) and high (0.700) confidence thresholds.

Module Detection Using MCODE Analysis



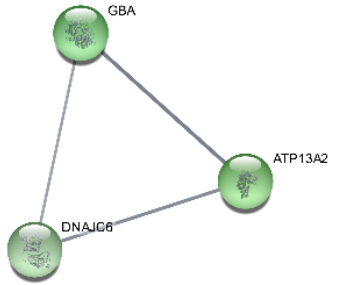
A Module 1

Dopaminergic–synaptic cluster



B Module 2

Mitochondrial-inflammatory cluster



C Module 3

Lysosomal cluster

Figure 4. MCODE-derived functional modules of the PD–LID interaction network.

Identification of Hub Genes

Topological analysis of the PPI network using the MCC algorithm identified fifteen hub genes:

PINK1	NLRP3	EIF2AK2
TH	IL10	NLRC4
NTRK1	ATP13A2	IRS1
CASP8	DRD1	DRD2
SNCA	PARK2	FOSB

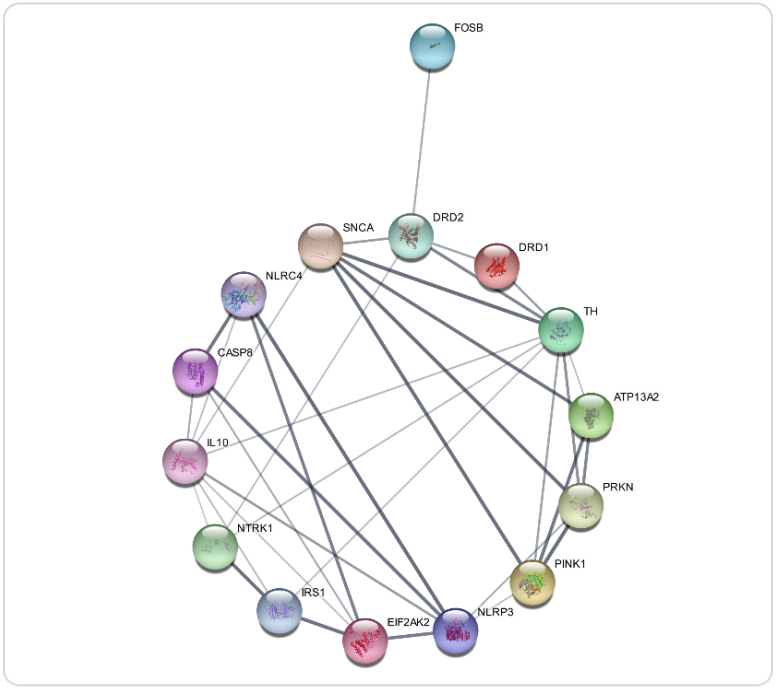


Figure 5. Hub gene identification using CytoHubba in Cytoscape.

KEGG Pathway Enrichment (1 of 3)

1 Dopaminergic & neuroactive ligand–receptor signalling

KEGG enrichment identified several pathways associated with dopaminergic signalling and neuroactive ligand-receptor interactions.

KEGG Pathway	Adjusted p-value	Key Genes
Dopaminergic synapse	< 0.01	DRD1, DRD2, DRD3, TH
Neuroactive ligand-receptor interaction	< 0.01	DRD1, DRD2, DRD3, ADORA2A, PDYN, PENK
cAMP signalling pathway	< 0.05	DRD1, DRD2, ADORA2A, RYR2
Calcium signalling pathway	< 0.05	DRD1, DRD2, CACNA1E, RYR2

2 Parkinson's disease & neurodegeneration

KEGG analysis identified enrichment in pathways associated with neurodegenerative diseases.

KEGG Pathway	Adjusted p-value	Key Genes
Parkinson disease	< 0.01	PINK1, TH, ATP13A2, DRD2
Pathways of neurodegeneration multiple diseases	< 0.01	CASP8, PINK1, MFN2, NLRP3
Alzheimer disease	< 0.05	CASP8, CAT, STAT1
Huntington disease	< 0.05	CASP8, DCTN1, PPARG
Amyotrophic lateral sclerosis	< 0.05	PINK1, DCTN1

KEGG Pathway Enrichment (2 of 3)

3 Mitochondrial dysfunction, mitophagy & metabolism

KEGG enrichment also identified pathways related to mitochondrial function and metabolism.

KEGG Pathway	Adjusted p-value	Key Genes
Mitophagy-animal	< 0.05	PINK1, MFN2
Peroxisome	< 0.05	CAT, IDH1
Metabolic pathways	< 0.05	IDH1, CAT, GCH1
Fatty acid metabolism	< 0.05	MECR, PPARG
Longevity regulating pathway	< 0.05	CAT, IRS1, PPARG

4 Neuroinflammation & immune signalling

Immune activation and inflammatory pathways were also enriched, including genes such as NLRP3, NLRC4, IL10, and CASP8, which are associated with immune signalling.

KEGG Pathway	Adjusted p-value	Key Genes
NOD-like receptor signalling pathway	< 0.01	NLRP3, NLRC4, CASP8
Cytokine-cytokine receptor interaction	< 0.05	IL10, IL1R1, CXCR4
TNF signalling pathway	< 0.05	CASP8, FASLG
JAK-STAT signalling pathway	< 0.05	STAT1, IL10
Toll-like receptor signalling pathway	< 0.05	CASP8, STAT1

KEGG Pathway Enrichment (3 of 3)

5 Synaptic plasticity & learning-related pathways

KEGG Pathway	Adjusted p-value	Key Genes
Cocaine addiction	< 0.05	DRD1, DRD2, PDYN
Amphetamine addiction	< 0.05	DRD1, DRD2, TH
Alcoholism	< 0.05	DRD1, DRD2, FOSB
Long-term depression	< 0.05	PLA2G4A, RYR2
Glutamatergic synapse	< 0.05	HOMER1, PLA2G4A

KEGG analysis also identified pathways associated with synaptic plasticity and neural signalling, involving genes of synaptic signalling and neuronal plasticity.

GO-BP: Dopaminergic Neurotransmission

GO Term	Adjusted p-value	Key Genes
Synaptic transmission, dopaminergic	1.61E-06	DRD2, DRD3, TH, ADORA2A, DRD1
Regulation of dopamine uptake	8.23E-07	DRD2, DRD3, DRD1, GDNF
Dopamine metabolic process	3.39E-03	DRD2, DRD3, DRD1
Dopamine biosynthetic process	5.64E-03	TH, DRD2
Phospholipase C-activating dopamine signalling	7.75E-04	DRD1, DRD2, DRD3

Key regulators

TH

DRD1

DRD2

DRD3

The enriched gene set includes key regulators such as TH, DRD1, DRD2 and DRD3, which are associated with dopaminergic neurotransmission.

GO-BP: Neuroinflammation & Immunity

GO Term	Adjusted p-value	Genes
Inflammatory response	1.98E-03	NLRP3, IL1R1, IL10, REL, CXCR4
Regulation of innate immune response	4.79E-03	CASP8, PTPN22, FCGR2B
Response to lipopolysaccharide	1.37E-04	CASP8, IL10, TH, FASLG
Positive regulation of cytokine production	3.29E-03	REL, NLRP3, CXCR4
Regulation of immune effector process	4.11E-03	NLRC4, IL10

Key regulators

NLRP3 IL10 CASP8 NLRC4

Immune and inflammatory processes were significantly enriched. Key mediators include NLRP3, IL10, CASP8 and NLRC4, which are associated with immune signalling pathways.

GO-BP: Apoptosis, Mitophagy & Survival

GO Term	Adjusted p-value	Genes
Regulation of neuron apoptotic process	5.00E-04	PINK1, GDNF, NMNAT1
Apoptotic process	2.84E-03	CASP8, FASLG, STAT1
Mitophagy	1.55E-02	PINK1, ATG7, MFN2
Cellular response to hypoxia	2.00E-03	PINK1, PPARG
Negative regulation of mitochondrial fission	3.87E-03	PINK1, PPARG

Key regulators

PINK1 CASP8 MFN2

Processes related to apoptosis and mitochondrial regulation were also enriched, with genes such as PINK1, CASP8 and MFN2 associated with mitochondrial function and cell survival pathways.

GO-CC: Cellular Component

Enrichment of genes localized to neuronal, synaptic, mitochondrial, and immune-related cellular compartments.

Neuronal and synaptic structures

GO Term	Adjusted p-value	Genes
Axon	1.91E-08	DRD2, TH, SCN1A
Dendrite	1.72E-04	DRD2, TH, ADORA2A
Synapse	9.35E-04	DRD2, DRD3, TH
GABAergic synapse	5.67E-04	GAD1, SLC6A1
Presynaptic membrane	8.48E-03	DRD2, DRD1, ADORA2A
Dendritic spine	1.30E-02	DRD2, DRD1

Mitochondrial and immune structures

GO Term	Adjusted p-value	Genes
Mitochondrion	2.23E-03	PINK1, CASP8, MFN2
Canonical inflammasome complex	2.06E-02	NLRP3, NLRC4
Caveola	7.84E-03	CAV3, FASLG
Peroxisome	3.33E-02	CAT, IDH1
Protein-containing complex	2.25E-02	CASP8, STAT1

GO-MF: Molecular Function

GO Term	Adjusted p-value	Genes
Dopamine receptor activity	1.73E-04	DRD2, DRD3, DRD1
Opioid receptor binding	5.11E-03	PENK, PDYN
TNF receptor binding	1.06E-02	CASP8, FASLG
CXCR4 receptor activity	4.10E-02	CXCR4
Tyrosine monooxygenase activity	4.10E-02	TH
Protein homodimerization	5.90E-03	PINK1, STAT1
Enzyme binding	4.02E-03	CAT, RYR2

GO-MF analysis revealed enrichment of receptor activities and enzyme-related functions.

Hub Genes Grouped by Functional Theme

Dopaminergic signalling & receptor activity

TH DRD1 DRD2

Mitochondrial homeostasis & dysfunction

PINK1

Synaptic plasticity & metabolic pathways

ATP13A2 IRS1

Neuroinflammation, immune activation & oxidative stress response

NLRP3 EIF2AK2 SNCA NLRC4 NTRK1

Apoptosis, mitophagy & cell survival

PARK2 FOSB IL-10 CASP8

Phytochemical Screening

PASS prediction, ADMET filtering and molecular docking

PASS-Based Screening (1 of 3)

Anti-dyskinetic (Pa>Pi)	Pa
Dihydroberberine (Berberis) IMPHY000253	**0.8485**
2,3-Dihydrobenzofuran	**0.8196**
3-Carene	**0.8087**
Butylated hydroxytoluene	**0.7897**
Camphene hydrate	**0.7855**

Antiparkinsonian (Pa≥Pi)	Pa
Withanolide A (Ashwagandha)	**0.7224**
Angelicin (Jatamansi)	**0.5158**
2-Pentylfuran (Ginseng)	**0.5069**
2-Heptylfuran (Ginseng)	**0.5069**
Nicotine (Bacopa, Ashwagandha)	**0.4966**

Anti-inflammatory (Pa>Pi)	Pa
Hydrocortisone sodium succinate	**0.9322**
Solasodine	**0.9254**
Madecassic acid	**0.9203**
Madecassic acid (ID 73412)	**0.9203**
Asiatic acid (ID 119034)	**0.9185**

Rigidity relieving (Pa>Pi)	Pa
Ergosterol (Ginkgo, Ginseng, Ashwagandha)	**0.6430**
Butyl ethyl ether (Ginseng)	**0.6201**
1-Ethoxypentane (Ginseng)	**0.6042**
Stigmasterol (Ginkgo, Ashwagandha, Brahmi, Curcumin, Bacopa)	**0.5792**
Stigmasterol	**0.5792**

PASS-Based Screening (2 of 3)

Antineurotoxic (Pa>Pi)	Pa
Silibinin (Panax ginseng)	**0.9844**
Aromadendrin (Ginkgo)	**0.9624**
(−)-Epicatechin (ID 72276)	**0.9279**
Cianidanol (ID 9064)	**0.9279**
Cianidanol (Ginkgo biloba)	**0.9279**

Antiparkinsonian, tremor relieving (Pa>Pi)	Pa
Angelicin (Jatamansi) IMPHY000575	**0.5239**
Convolamine (ID 420422)	**0.5198**
N,N-Dimethyltryptamine	**0.5095**
Convolvidine (ID 4639600)	**0.5030**
Tropine (Ashwagandha) IMPHY010143	**0.4956**

Antioxidant (Pa>Pi)	Pa
Ginkgo biloba terpene trilactone (1)	**0.9917**
Ginkgo biloba terpene trilactone (2)	**0.9892**
Ginkgo biloba terpene trilactone (3)	**0.9883**
Ginkgo biloba terpene trilactone (4)	**0.9846**
Ginkgo biloba terpene trilactone (5)	**0.9778**

Dopamine D1 agonist (Pa>Pi)	Pa
Catechol (Ginkgo) IMPHY004079	**0.3772**
Dopamine	**0.2754**
Cirsilineol (ID 162464)	**0.1335**
Quercetin (Ginkgo) IMPHY004619	**0.1321**
Quercetin (ID 5280343)	**0.1321**

PASS-Based Screening (3 of 3) and ADMET Filtering

Movement disorders treatment (Pa>Pi)	Pa
(−)-Epicatechin (ID 72276)	**0.5160**
Squalene (Ginseng) IMPHY006486	**0.2255**
Guduchi IMPHY003499	**0.2176**
Ubiquinone (Ginseng) IMPHY000109	**0.1967**
Hygrine (Ashwagandha) IMPHY003462	**0.1946**

ADMET profiling

20 ▸ **14**

identified after PASS — met ADMET criteria

After PASS analysis with embedded PharmaExpert screening, 20 phytoconstituents were initially identified, of which 14 compounds satisfied the ADMET screening criteria and were selected for further analysis.

ADMET-Filtered Phytochemicals (1 of 2)

Phytoconstituent (ID)	Plant	OB ≥ 0.30	MW (Da)	TPSA (Å²)	SlogP	logS	QED	Lipinski	BBB
Sesamin (IMPHY014895)	Ginkgo biloba	0.6575	354.358	55.38	3.2192	-4.56	0.82	Accept	0.9644
Dihydroberberine (IMPHY000253)	Berberis vulgaris	0.3894	337.375	40.16	3.3023	-4.44	0.84	Accept	0.9916
2,3-Dihydrobenzofuran (IMPHY001223)	Brahmi	0.8505	120.151	9.23	1.6215	-2.92	0.50	Accept	0.9773
Pinoresinol (IMPHY003715)	Jatamansi	0.5213	358.39	77.38	3.1902	-2.43	0.87	Accept	0.6458
Butylated hydroxytoluene (IMPHY003392)	Ginseng, Curcumin	0.3127	220.356	20.23	4.29562	-4.95	0.69	Accept	0.9323
Camphene hydrate (IMPHY009740)	Curcumin	0.8211	154.253	20.23	2.1935	-2.20	0.56	Accept	0.9912
4'-Methylacetophenone (IMPHY007069)	Curcumin	0.4826	134.178	17.07	2.19762	-1.37	0.53	Accept	0.8389

Table 4. ADMET-filtered phytochemicals with blood–brain barrier (BBB) permeability. All 14 compounds are Lipinski-compliant (Accept).

ADMET-Filtered Phytochemicals (2 of 2)

Phytoconstituent (ID)	Plant	OB ≥ 0.30	MW (Da)	TPSA (Å²)	SlogP	logS	QED	Lipinski	BBB
Gomisin N (IMPHY004134)	Ginseng	0.4844	400.471	55.38	4.4875	-4.93	0.75	Accept	0.9911
Oxyberberine (IMPHY000342)	Berberis vulgaris	0.6006	351.358	58.92	2.9705	-5.13	0.71	Accept	0.9726
Besigomsin (IMPHY010599)	Ginseng	0.8911	416.47	75.61	3.6024	-3.59	0.81	Accept	0.9384
Angelicin (IMPHY000575)	Jatamansi	0.7305	186.166	43.35	2.5392	-3.18	0.50	Accept	0.9925
Nicotine (IMPHY007301)	Withania somnifera, Mucuna pruriens, Bacopa monnieri	0.7935	162.236	16.13	1.8483	0.85	0.62	Accept	0.9445
2-Pentylfuran (IMPHY005811)	Ginseng	0.4579	138.21	13.14	3.0123	-3.99	0.58	Accept	0.9835
Withasomnine (IMPHY004857)	Withania somnifera	0.7933	184.242	17.82	2.4963	-3.30	0.66	Accept	0.9869

Table 4. ADMET-filtered phytochemicals with blood–brain barrier (BBB) permeability. All 14 compounds are Lipinski-compliant (Accept).

Molecular Docking: Binding Energies (1 of 2)

Ligand	PINK1 6EQI	NLRP3 6NPY	EIF2AK2 2A19	TH 2XSN	IL-10 2ILK	NLRC4 4KXF	NTRK1 5JFS	ATP13A2 7VPI	IRS1 1QQG	CASP8 6X8H	DRD1 8JXR	DRD2 6CM4	SNCA 3Q28	PARK2 8W31	FOSB 9OC3
★ **IMPHY000253** Dihydroberberine	-3.4	**-9.0**	-8.9	**-10.1**	-6.1	**-9.1**	**-10.3**	**-9.0**	-3.8	-7.8	**-9.33**	**-9.6**	-8.6	-6.2	-4.9
★ **IMPHY000342** Oxyberberine	-3.0	-8.7	-8.8	**-9.6**	-6.0	**-9.6**	**-9.6**	**-9.2**	-3.0	-7.6	**-9.3**	**-9.8**	-8.5	-6.3	-5.1
IMPHY000575 Angelicin	-5.1	-7.5	-7.1	-7.5	-5.5	-7.6	-7.9	-7.9	-3.8	-6.1	-8.0	-7.6	-7.9	-5.7	-4.1
IMPHY001223 2,3-Dihydrobenzofuran	-4.2	-5.9	-5.7	-5.2	-3.9	-5.7	-6.3	-5.8	-3.6	-4.7	-5.8	-6.3	-5.7	-5.3	-3.1
IMPHY003392 Butylated hydroxytoluene	-2.4	-7.4	-7.4	-7.0	-5.9	-7.8	-8.2	-7.0	-4.4	-5.7	-7.4	-6.9	-8.1	-5.3	-3.8
IMPHY003715 Pinoresinol	-3.3	-7.5	-8.1	**-9.6**	-6.2	**-9.0**	-8.1	**-9.1**	-3.1	-7.1	-8.9	-8.8	-8.4	-6.0	-4.0
IMPHY004134 Gomisin N	-2.9	-4.0	-8.0	-6.3	-6.3	-8.9	**-9.2**	-7.2	-2.0	-6.8	-8.7	-8.5	-7.9	-6.3	-4.1

Docking energy (kcal/mol): **≤ −9.0** | **−9.0 to −7.0** | **−7.0 to −5.0** | **> −5.0** ★ top-ranked

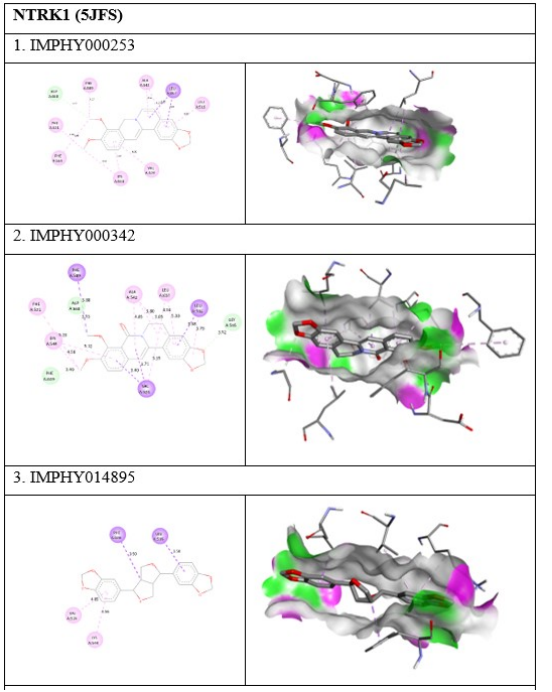
Molecular Docking: Binding Energies (2 of 2)

Ligand	PINK1 6EQI	NLRP3 6NPY	EIF2AK2 2A19	TH 2XSN	IL-10 2ILK	NLRC4 4KXF	NTRK1 5JFS	ATP13A2 7VPI	IRS1 1QQG	CASP8 6X8H	DRD1 8JXR	DRD2 6CM4	SNCA 3Q28	PARK2 8W31	FOSB 9OC3
IMPHY004857 Withasomnine	-4.2	-7.4	-7.2	-7.3	-5.0	-7.8	-8.5	-7.2	-4.2	-6.0	-7.2	-8.7	-7.8	-6.4	-4.2
IMPHY005811 2-Pentylfuran	-3.7	-5.2	-5.2	-5.2	-3.7	-5.4	-5.6	-5.2	-3.5	-4.3	-5.7	-5.8	-5.5	-4.7	-2.9
IMPHY007069 4'-Methylacetophenone	-4.7	-6.0	-5.9	-5.9	-4.6	-6.2	-6.7	-6.2	-3.8	-5.3	-6.2	-6.6	-6.4	-4.6	-3.6
IMPHY007301 Nicotine	-3.3	-6.0	-5.8	-6.0	-4.3	-6.3	-6.4	-5.7	-3.4	-4.8	-6.0	-7.7	-6.4	-5.1	-3.6
IMPHY009740 Camphene hydrate	-2.9	-6.3	-5.8	-5.7	-4.3	-6.0	-5.4	-5.4	-3.3	-4.4	-5.8	-5.3	-6.3	-4.1	-3.3
IMPHY010599 Besigomsin	-2.8	-4.1	-7.9	-5.7	-5.7	-7.9	-8.4	-8.7	-4.8	-6.8	-7.3	-8.9	-7.7	-5.8	-4.2
★ IMPHY014895 Sesamin	-3.9	-7.8	-8.8	**-10.2**	-6.7	**-9.7**	**-10.6**	**-9.6**	-4.3	-7.6	**-10.0**	**-10.4**	-8.7	-6.2	-4.6

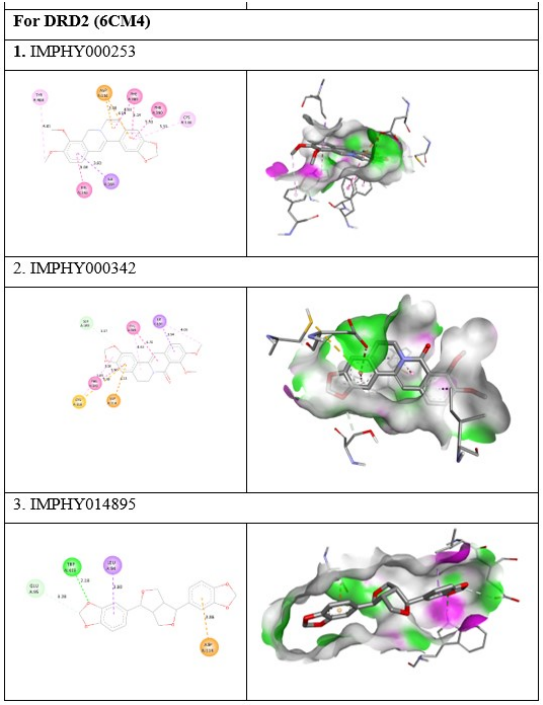
Docking energy (kcal/mol): **≤ −9.0** | **−9.0 to −7.0** | **−7.0 to −5.0** | **> −5.0**

★ top-ranked

Docking Poses of Top-Ranked Compounds



NTRK1 (5JFS)



DRD2 (6CM4)

Top-ranked ligands

1. **IMPHY000253**
   Dihydroberberine
2. **IMPHY000342**
   Oxyberberine
3. **IMPHY014895**
   Sesamin

Binding Affinity Profile of Top-Ranked Compounds

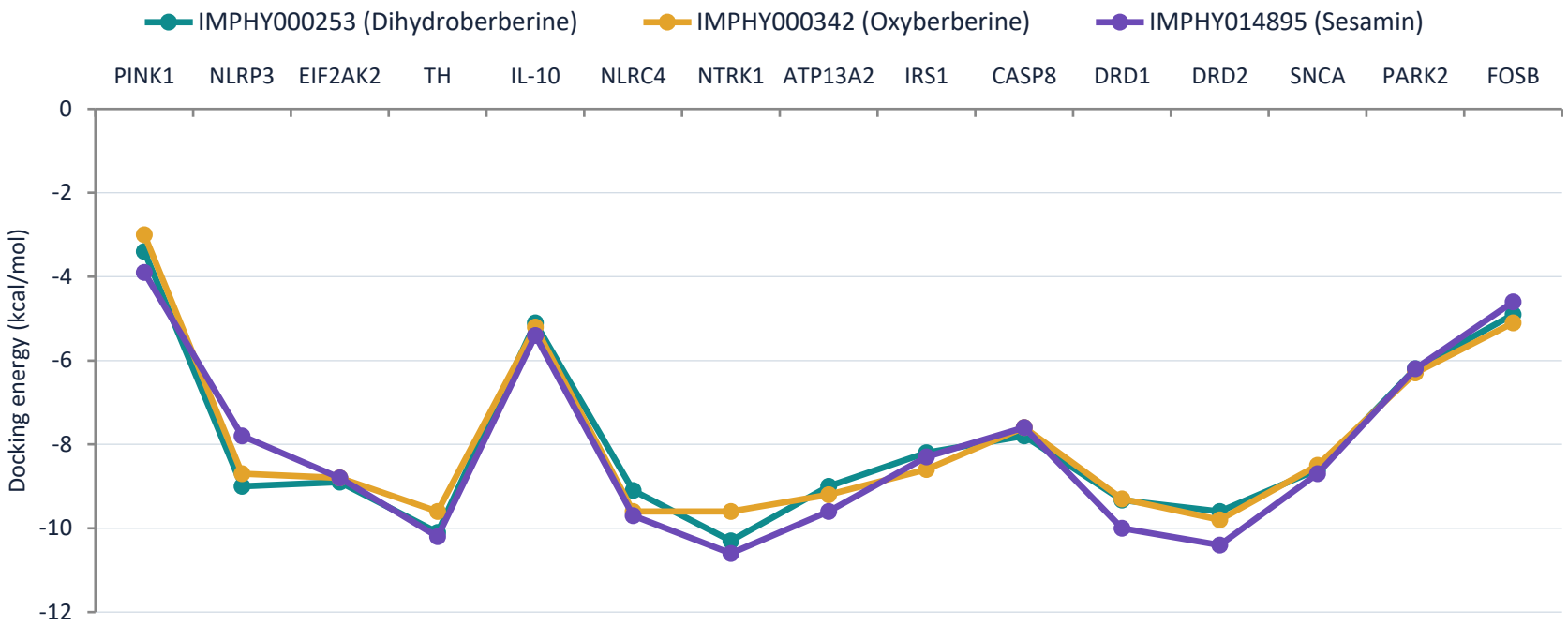


Figure 6. Comparative binding affinity profile of the top-ranked phytochemicals (Oxyberberine, Dihydroberberine and Sesamin) against PD–LID hub targets. More negative = stronger predicted binding.

Residue-Level Interactions: NTRK1 (5JFS)

Ligand	Docking score (kcal/mol)	Type of bonding	Interacting amino acids
IMPHY000253	**−10.3**	Carbon hydrogen bond	Asp668
		Alkyl	Ala542, Phe589, Phe521, Phe669
		π-Alkyl	Leu516, Ala542, Val524, Lys544
		π-Sigma	Leu657
IMPHY000342	**−9.6**	Carbon hydrogen bond	Asp668, Phe669, Gly595
		Alkyl	Phe521, Leu657
		π-Alkyl	Lys544, Leu657
		π-Sigma	Leu516, Val524, Phe589
IMPHY014895	**−10.6**	π-Alkyl	Val524, Lys544
		π-Sigma	Phe669, Leu516

Residue-Level Interactions: DRD2 (6CM4)

Ligand	Docking score (kcal/mol)	Type of bonding	Interacting amino acids
IMPHY000253	**-9.6**	π-Alkyl	Tyr408, Cys118
		π-Sigma	Ile184
		π-Anion	Asp114
		π–π T-shaped	Phe389, Phe390, His393
IMPHY000342	**-9.8**	Carbon hydrogen bond	Ser193
		Alkyl	Ile184, Phe389, Cys118
		π-Sigma	Ile184
		π-Anion	Asp114
		π-Sulfur	Cys118
		π–π T-shaped	Phe389, Phe390
IMPHY014895	**-10.4**	Conventional hydrogen bonding	Trp413
		Carbon hydrogen bond	Glu95
		π-Sigma	Leu94
		π-Anion	Asp114

Conclusion

Sesamin | **Dihydroberberine** | **Oxyberberine**

Three promising phytoconstituents

Key findings

Identified through integrated PASS prediction, ADMET profiling and molecular docking. The compounds show favourable drug-likeness and significant binding affinity toward multiple PD-LID hub targets in dopaminergic signalling, neuroinflammation, mitochondrial dysfunction and synaptic plasticity.

Way forward

The identified hub genes may serve as potential biomarkers and therapeutic targets for understanding the progression of Parkinson's disease and levodopa-induced dyskinesia, and will be explored further in in-vitro and in-vivo studies to validate their pathological significance.

Thank you

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Acknowledgement

The authors gratefully acknowledge Dr. V. V. Poroikov and the Institute of Biomedical Chemistry (IBMC), Russian Academy of Medical Sciences, Moscow, for providing free access to the PASS software used for the prediction of biological activity spectra in this study.

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