TheGMS
The Gazette of Medical Sciences
https://www.thegms.co ISSN 2692-4374 DOI https://www.doi.org/10.46766/thegms

Neurology | Research

Drug Repurposing for Parkinson's Disease with Deep Learning: A Virtual Screening Approach

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Submitted: 01 August 2026
Approved: 20 August 2026
Published: 21 August 2026

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How to cite this article: Vokkarne K, Sundararajan R. Drug Repurposing for Parkinson's Disease with Deep Learning: A Virtual Screening Approach. G Med Sci. 2026; 7(1):43-59. https://www.doi.org/10.46766/thegms.neuro.26010801

ABSTRACT

This paper investigates Drug Repurposing for Parkinson's Disease with Deep Learning. The methodology used is Drug Discovery via Virtual Screening. Various existing drugs were screened and binding scores obtained to find potential efficacy that may inhibit Parkinson's Disease. An end-to-end Drug Repurposing pipeline was built for the study. We observe that Metformin, a widely administered Type-2 diabetes drug, Remdesivir an anti-viral drug and Simvastatin, a cholesterol drug, performed best with high binding scores on selected targets when compared to the FDA approved Parkinson's drug Levodopa. In addition, Curcumin, a natural turmeric ingredient, also had high binding scores. The drugs identified had high efficacy for Parkinson's SCNA and PINK1 targets. The research involved three different Deep Learning models on two benchmark datasets, namely KIBA and DAVIS. The methodology using Deep Learning was carried out after developing custom Python scripts that run on a Jupyter Notebook. The PD targets were further compared with a String diagram to identify the strength of interactions between them. The results also show strong potential when repurposed drugs are used along with existing FDA approved drugs for Parkinson's Disease. Further research can be performed with in vivo clinical studies.

KEYWORDS

Drug Repurpose, Parkinson's Disease, Deep Learning, Virtual Screening

INTRODUCTION

Drug Repurposing involves finding new treatments using drugs that already exist [1]. It can offer immense benefits due to the comprehensive wealth of information that already exist about pharmacokinetics, safety data, toxicity, and other factors in humans. One of the main pros is reduction in time and amount to discover new applications, due to its low risk, high reward approach compared to conventional drugs discovery methods [2]. One example is the influenza drug, amantadine that was accidentally discovered to improve Parkinson's symptoms and help reduce tremor and dyskinesia and often used in conjunction with levodopa the standard drug for Parkinson's Disease [3].

Drug repurposing involves the use of active compounds for a new therapeutic purpose from that originally indicated [4]. While drug repurposing offers a promising, fast, and cost-effective path to new treatments, the drugs discovered still need to go thorough preclinical evaluation to assess their efficacy and prove that they can address the specific neurodegenerative mechanisms of the disease. Virtual Screening (VS) involves identifying compounds that bind to a target such as enzyme or receptor from a large library of compounds using computational techniques [5].

Parkinson's Disease is a progressive movement disorder of the nervous system [6]. It can cause problems with movement, stiffness, tremor, and balance due to nerve cell damage or weakening. A person with Parkinson's Disease may find it hard to walk, talk or even complete simple tasks.

As per National Institute of Neurological Diseases [6], there are three stages of Parkinson's Disease:

- Early Stage: Mild symptoms, not necessarily affecting daily life.
- Moderate Stage: Symptoms often affect movement on both sides of the body. Balance issues are observed.
- Advanced State: Significant daily limitations, often requiring assistance for movement and daily tasks.

In addition to the primary symptoms, there are a variety of secondary symptoms, such as mental and emotional problems, speech changes, difficulty swallowing, sleep, and cognitive issues. According to Yang, H. et al., Parkinson's Disease (PD) will increase from 11.77 million in 2021 to 25.2 million cases by 2050, potentially becoming the fastest-growing neurological disorder and a global health challenge [7].

As per Mammen, J.R., *et al.* mobility, safety, interpersonal interactions, social, and family relations are impacted from a social perspective leading to lost independence, making life a struggle [8].

Various factors are linked to who can get or likely to get PD. The main ones are listed by National Institute of Neurological Diseases [6].

The average age of early onset is mid 60s and can increase significantly with age. Men are more likely to get PD than women. Genetics could play a role in PD as hereditary in family has been shown to increase incidence.

Environmental scenarios and exposure to rural settings and pesticides have shown to increase cases. Dopamine, the chemical that signals nerve cells movement starts to die in a Parkinson's patient. Since PD is a neurogenerative disorder and a progressive illness, symptoms often worsen over time [9]. Figure 1 shows that brain cells in green as PD progresses.

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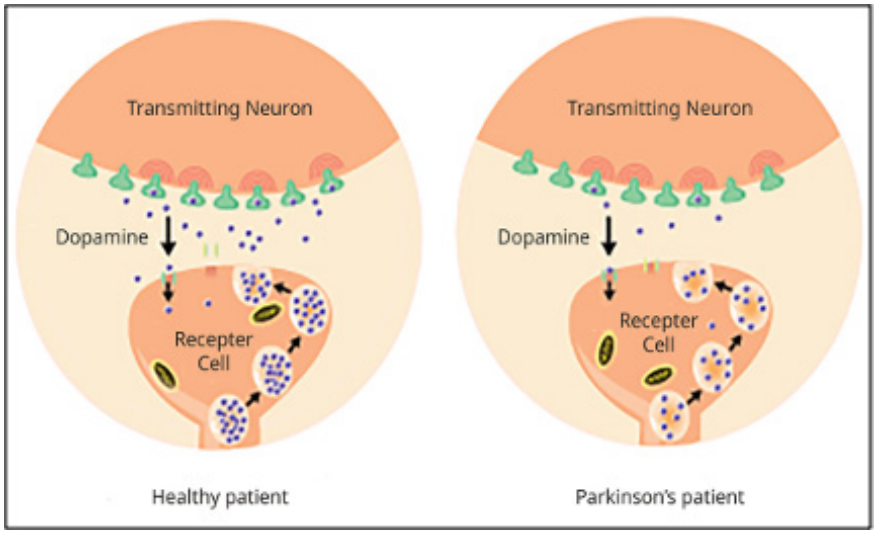

Figure 1. Comparison of Dopamine Production of Healthy vs. Parkinson's Patient [9].

Certain lifestyle factors have been shown to act as protective agents to PD. Two most significant factors include smoking and caffeine use [6]. Studies show nicotine acting as a dopamine release agent and caffeine use, which can act as antagonist of adenosine A2a receptor, which plays a neuroprotective role by blocking this receptor. Ibuprofen use and exercise are some other associations that have shown benefits.

The genes most commonly associated with PD include SNCA, LRRK2, DJ-1, PRKN, PINK1, and GBA [6]. There is currently no known disease-modifying therapy for Parkinson's disease (PD). However, several symptomatic treatment options are available, primarily based on dopaminergic replacement therapy with levodopa and carbidopa, which remain among the most widely used treatments, as well as dopamine agonists such as pramipexole and ropinirole [10]. There are some advances and Tavapadon, a new, once-daily drug for Parkinson's disease developed by AbbVie, is expected to receive FDA approval decisions in the first half of 2026. Several studies point to early treatment as crucial for managing the symptoms. Surgery is sometimes required in complicated cases [6].

We used deep learning to analyze Parkinson's Disease sequences and identify the relevant genetic pathway, which was subsequently targeted through virtual screening. This has a tremendous potential for rapid drug discovery over traditional labor-intensive screening processes, which are cost and time consuming [11]. A computationally driven process for drug repurposing shown in **Figure 2** depicts the various stages from disease and target identification to virtual screening drugs for drug identification and testing.

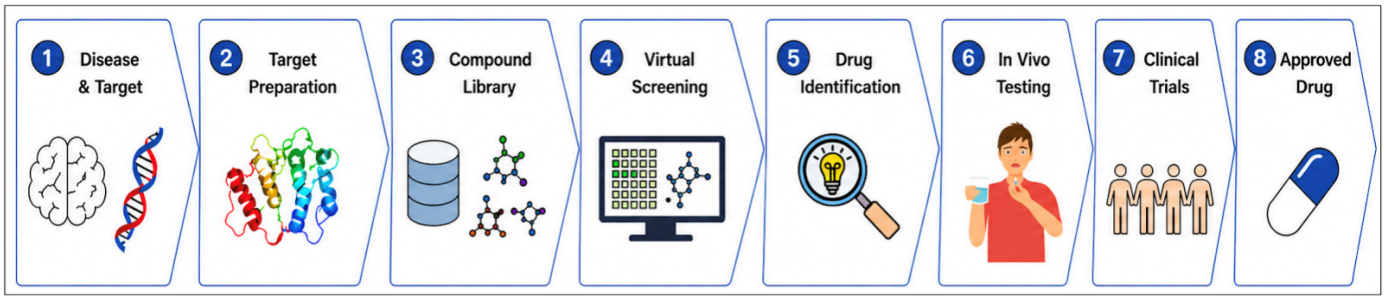

Figure 2. Computationally driven process for Drug Repurposing with AI/DL Multistage process from disease target preparation to drug discovery and approval

Vokkarne K, Sundararajan R. Drug Repurposing for Parkinson's Disease with Deep Learning: A Virtual Screening Approach. G Med Sci. 2026; 7(1):43-59. https://www.doi.org/10.46766/thegms.neuro.26010801

AI tools, such as DeepPurpose, learn from large, curated datasets that contain experimentally validated interactions: for example (BindingDB, DAVIS and KIBA) to make predictions [12]. They use advanced representations that capture structural and chemical properties of drugs and targets [13]. The library uses neural network models, such as Graph Neural Networks and Convolutional Neural Networks for protein sequences and learn from embedding to arrive at biochemical interactions [14].

DeepPurpose leverages models trained in Drug-Target Interaction (DTI) and datasets allow them to perform rapid virtual screening of drugs to arrive at interaction scores. DeepPurpose supports over 15 compound and protein encoders, such as Morgan fingerprints to transformers and convolutional neural networks (CNNs). These helps translate chemical SMILES strings and amino acid sequences to numerical values that represent atomic structures. It also predicts binding affinities such as IC50 values, which can be measured in a wet-lab to associate patterns.

Structural Consistency is based on molecular graph representation using Graph Neural Networks (GNNs) based methods to determine drug binding and models that use visualizations of learned embedding's that group drugs to meaningful biological clusters [15].

MATERIALS AND METHODS

A. Drug Repurposing Pipeline

A structured approach to drug repurposing was used, with an end-to-end pipeline (**Figure 3**). The steps involved include PD Target Selection, Drug Candidate Library and Drug Selection, Data Preparation, Binding Scores Prediction, Score Calibration, Biological Filtering, Multifactor Ranking, and finally published Drug Repurposing Results.

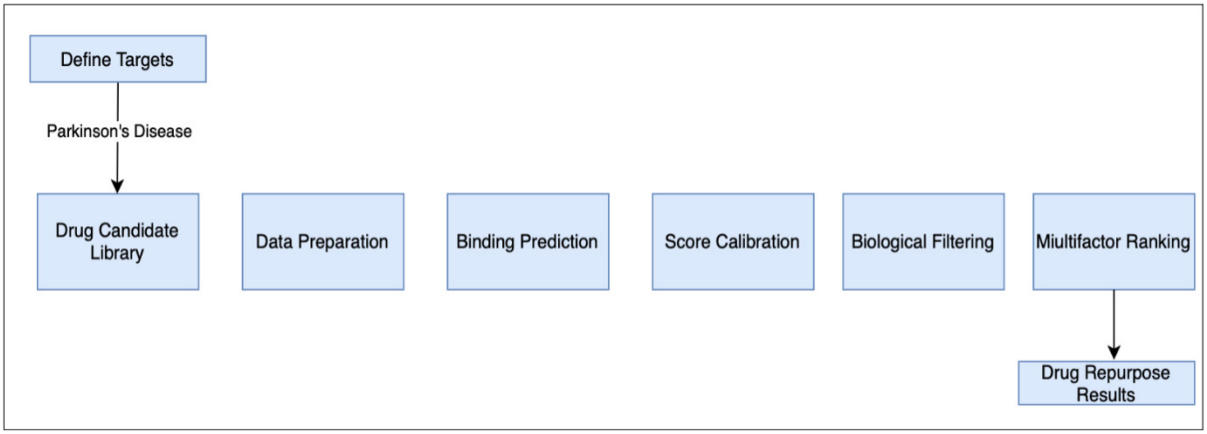

Figure 3. Drug Repurposing End-To-End Pipeline and Steps Involved

B. Drug Target Selection

The first step is to identify the PD targets. We selected five most common targets for PD and their associated sequences from various sources such as NIH. The identified genes were "SNCA", "PINK1", "PRKN", "PARK7", and "LRRK2" [5]. SNCA gene makes the protein alpha-synuclein that help nerves to communicate with each other. This was the very first gene for PD to be identified [16], PINK1 gene makes the protein that detects any damage to cell mitochondria [17-18]. The PRKN gene helps cells remove damaged mitochondria by making protein called parkin. Any changes in this protein causes

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early onset of PD [17-18]. Similarly, PRK7 and LRRK2 are also help control important cell processes.

C. Drug Candidate List

Various drugs were studied and screened as part of this research to determine efficacy to the Parkinson's targets. The drugs studied included GLP-1 receptors Exenatide and Lixisenatide, which are also known to reduce neuroinflammation and improve mitochondrial function [19]. Additionally, Metformin, a widely used drug for type 2 diabetes known to reduce oxidative stress; Ambroxol, a lysosomal pathway modulator commonly used as a cough medicine; Amantadine, an anti-influenza drug; Nilotinib and Ibuprofen, an NSAID with anti-inflammatory properties; Simvastatin and Rosuvastatin, cholesterol-lowering drugs; Paracetamol, an analgesic; antibacterial drugs used to treat meningitis; and Remdesivir, an anti-viral drug used for COVID-19, were also screened [20].

Table 1. Major Repurposed Drugs – Parkinson's Disease [3]

Drug	Original use	PD Link
Exenatide	Type-2 Diabetes	GLP-1 agonist, neuroprotection
Liraglutide	Diabetes	Anti-inflammatory, neuronal survival
Metformin	Diabetes	AMPK activation, mitochondrial support
Nilotinib	Leukemia	A-synuclein clearance
Isradipine	Hypertension	Calcium channel modulation
Ambroxol	Cough/Mucolytic	GCase enhancement
Ursodeoxycholic acid (UDCA)	Liver disease	Mitochondrial protection
Simvastatin	Hyperlipidemia	Anti-inflammatory, neuroprotective

The drugs studied also align with current area of research, the industry which is focused on drugs shown in Table I. Many of these drugs are being studied by Cure Parkinson's Trust (CPT) and international Linked Clinical Trials (iLCT) program which focuses on PD [21]. Remdesivir developed originally for Hepatitis-C drug and Ebola [21] was repurposed for COVID-19 is being studied for other repurpose uses.

D. Data Preparation

Once the drugs were identified, the Simplified Molecular input line entry system (SMILES) string for each drug was obtained from PubChem chemical library [22]. The Protein FASTA sequences for these Targets was then obtained from UniProt database [23] for "SNCA", "PINK1", "PRKN", "PARK7", and "LRRK2".

E. Binding Scores Prediction

DeepPurpose takes the compound's SMILES string and protein amino acid sequence pair as input [12]. The toolkit then takes the protein and compound embedding input into a decoder to generate predictions. The output includes how well the protein binds to a compound, indicated by generating the binding scores (including median inhibitory concentration (IC50)). The library internally uses up

Vokkarne K, Sundararajan R. Drug Repurposing for Parkinson's Disease with Deep Learning: A Virtual Screening Approach. G Med Sci. 2026; 7(1):43-59. https://www.doi.org/10.46766/thegms.neuro.26010801

to three different models to output the final scores. DeepPurpose uses two benchmark datasets, namely KIBA and DAVIS [12], to ensure generalization of results.

After installing DeepPurpose along with associated dependency modules, we created custom scripts for running it on a Jupyter Notebook. All the drugs were compared against a common FDA approved PD drug levodopa, a dopamine precursor drug used in managing PD. We used a pre-trained model from DeepPurpose along with the repurpose API. Binding scores were obtained after successful runs.

RESULTS

F. Running the model

Shown below are the repurposing sequences of runs and results for Metformin, Remdesivir, Simvastatin, and Curcumin. Also included are results for Levodopa for baseline comparison. Results are shown below for each step (We started with Metformin and then screened the other drugs in the same manner).

===== MODEL CONFIG =====

--- Running Repurposing for Target: SNCA ---
Loading customized repurposing dataset...
Beginning Downloading Pretrained Model...
Note: if you have already downloaded the pretrained model before, please stop the program and set the input parameter 'pretrained Dir' to the path
Dataset already downloaded in the local system...
Using pretrained model and making predictions...
repurposing...
Drug Target Interaction Prediction Mode...
in total: 1 drug-target pairs
encoding drug...
unique drugs: 1
encoding protein...
unique target sequence: 1
Done.
predicting...

Predictions from model 1 with drug encoding MPNN and target encoding CNN are done...
----
repurposing...
Drug Target Interaction Prediction Mode...
in total: 1 drug-target pairs
encoding drug...
unique drugs: 1

Vokkarne K, Sundararajan R. Drug Repurposing for Parkinson's Disease with Deep Learning: A Virtual Screening Approach. G Med Sci. 2026; 7(1):43-59. https://www.doi.org/10.46766/thegms.neuro.26010801

```
encoding protein...
unique target sequence: 1
Done.
predicting...
--------------
Predictions from model 2 with drug encoding CNN and target encoding CNN are done...
-------------
repurposing...
Drug Target Interaction Prediction Mode...
in total: 1 drug-target pairs
encoding drug...
unique drugs: 1
encoding protein...
unique target sequence: 1
Done.
predicting...
--------------
Predictions from model 3 with drug encoding Morgan and target encoding CNN are done...
-------------
repurposing...
Drug Target Interaction Prediction Mode...
in total: 1 drug-target pairs
encoding drug...
unique drugs: 1
encoding protein...
unique target sequence: 1
-- Encoding AAC takes time. Time Reference: 24s for ~100 sequences in a CPU.

Calculate your time by the unique target sequence #, instead of the entire dataset.
Done.
predicting...
--------------
Predictions from model 4 with drug encoding Morgan and target encoding AAC are done...
-------------
repurposing...
Drug Target Interaction Prediction Mode...
in total: 1 drug-target pairs
encoding drug...
unique drugs: 1
encoding protein...
unique target sequence: 1
```


Vokkarne K, Sundararajan R. Drug Repurposing for Parkinson's Disease with Deep Learning: A Virtual Screening Approach. G Med Sci. 2026; 7(1):43-59. https://www.doi.org/10.46766/thegms.neuro.26010801

```
-- Encoding AAC takes time. Time Reference: 24s for ~100 sequences in a CPU.

Calculate your time by the unique target sequence #, instead of the entire dataset.
Done.
predicting...
---------------
Predictions from model 5 with drug encoding Daylight and target encoding AAC are done...
-------------
models prediction finished...
aggregating results...
---------------
Drug Repurposing Result for SNCA
+------+-----------+-------------+---------------+
| Rank | Drug Name | Target Name | Binding Score |
+------+-----------+-------------+---------------+
| 1    | metformin |    SNCA     |   101217.23   |
+------+-----------+-------------+---------------+
--- Finished Repurposing for Target: SNCA ---
```

DISCUSSION

After running Deep Learning-based virtual screening, it was observed that Remdesivir, Metformin and Simvastatin had the highest scores (indicating best choice) compared to Levodopa, the approved drug for PD. In addition, Curcumin also had very good results.

The chemical structure of Remdesivir (**Figure 4**) and Simvastatin (**Figure 5**) are shown below.

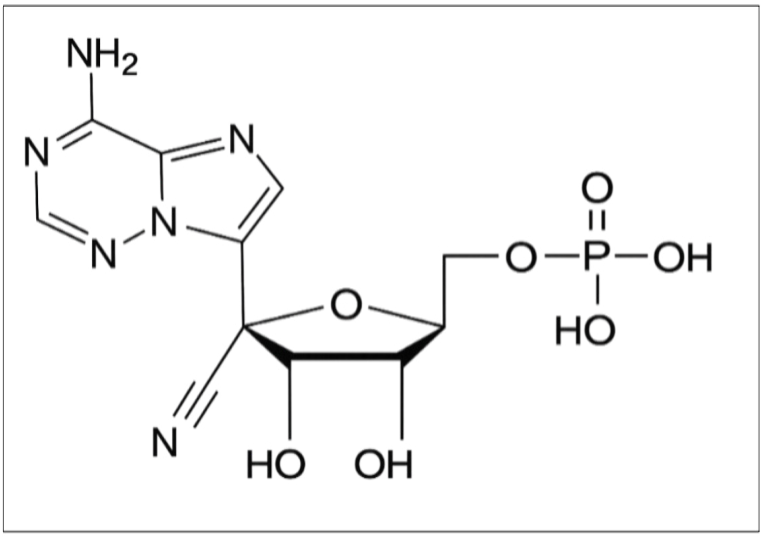

Figure 4. Remdesivir Chemical Structure.

Vokkarne K, Sundararajan R. Drug Repurposing for Parkinson's Disease with Deep Learning: A Virtual Screening Approach. G Med Sci. 2026; 7(1):43-59. https://www.doi.org/10.46766/thegms.neuro.26010801

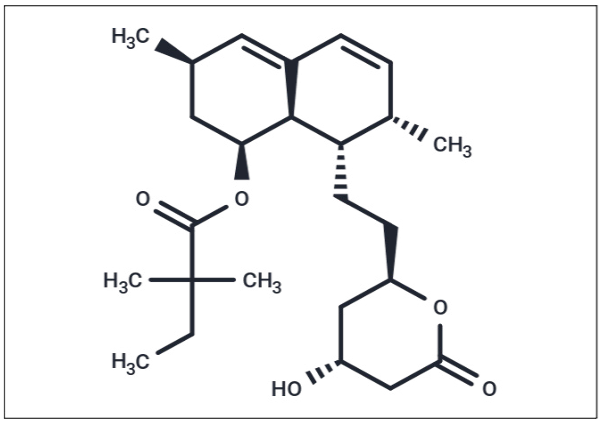

Figure 5. Simvastatin Chemical Structure.

Metformin is a biguanide type medication with molecular formula *C*4 *H*11 *N*5. **Figure 6** shows the chemical structure of Metformin. It contains two coupled guanidine molecules with two methyl groups attached to one of the terminal nitrogen atoms [24].

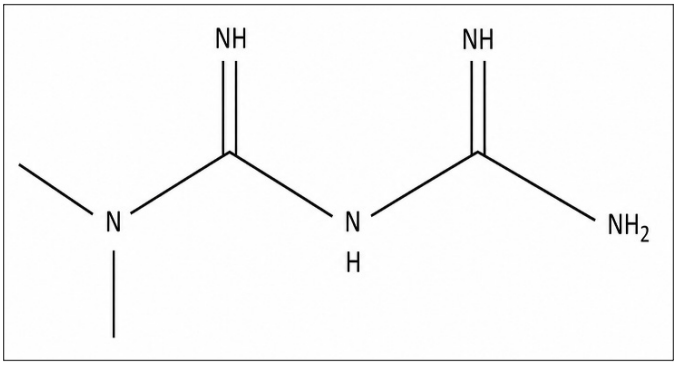

Figure 6. Metformin Chemical Structure.

Figure 7 shows the raw binding scores obtained for Metformin. It is observed that Metformin had good binding affinity scores for SNCA and PINK1 PD targets. SNCA has a score of 101217.23, which was the highest as seen in **Table 2**. This indicates strong results for Metformin and potential for further research into repurpose benefits for the drug.

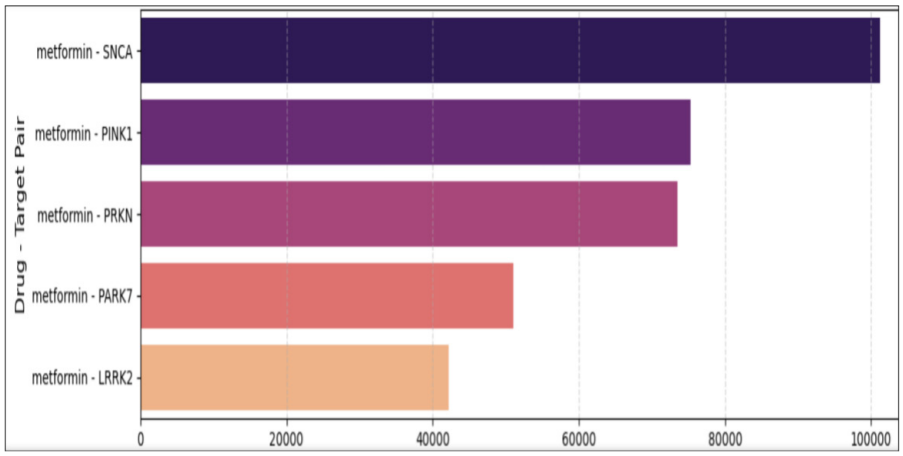

Figure 7. Metformin Raw Binding Scores for the five PD targets SNCA, PINK1, PRKN, PARK7 & LRRK2.

Vokkarne K, Sundararajan R. Drug Repurposing for Parkinson's Disease with Deep Learning: A Virtual Screening Approach. G Med Sci. 2026; 7(1):43-59. https://www.doi.org/10.46766/thegms.neuro.26010801

Table 2. Raw Binding Scores for Metformin

Drug Name	Target Name	Binding Score
Metformin	SNCA	101217.23
Metformin	PINK1	75289.03
Metformin	PRKN	73498.53
Metformin	PARK7	51009.94
Metformin	LRRK2	42149.58

A comparative analysis of the Metformin metrics was performed and below are some findings.

Mean Binding Score:

$$\mu = 1/n \sum_{\{i=1\}}^{\{n\}x} \text{xi}$$

μ = 68632.86

Standard Deviation:

$$\sigma = \sqrt{\left\{1/n \sum_{\{i=1\}}^{\{n\}} (xi - p)^2\right\}}$$

$\sigma = 21096.84$

This indicates moderate variability, with the strongest affinity observed for SNCA and lowest for LRRK2.

Coefficient of Variation (CV):

It is usually a model consistency indicator:

$CV=\frac{\sigma}{\mu}$ = ~0.307

A lower coefficient of variation shows a stronger multi target prediction.

Z-score Normalization for Metformin targets:

$$z = \frac{x-\mu}{\sigma} = \frac{1.2-0.0}{1.0} = 1.2$$

Figure 8. Metformin Z-score normalization curve for PD targets.

G. Score Calibration

Similar to Metformin, a drug repurposing scan was performed with Simvastatin, Remdesivir and Curcumin. Remdesivir and Simvastatin showed promising results for SNCA and PINK1 targets. Curcumin also had very good binding scores for SNCA and PINK1. The target LRRK2 had the lowest raw binding affinity scores for all drugs. These drugs were then compared to Levodopa, the FDA-approved drug. These results were normalized with respect to the SNCA value of metformin. **Table 3** shows the normalized scores.

Vokkarne K, Sundararajan R. Drug Repurposing for Parkinson's Disease with Deep Learning: A Virtual Screening Approach. G Med Sci. 2026; 7(1):43-59. https://www.doi.org/10.46766/thegms.neuro.26010801

TABLE 3. Normalized Binding Scores for All Four Drugs

Target	Binding Score				
	Metformin	Remdesivir	Simvastatin	Curcumin	Levodopa
SNCA	1.000	1.193	0.227	2.051	2.007
PINK1	0.744	1.175	0.201	1.596	1.722
PRKN	0.726	1.076	0.178	1.462	1.366
PARK7	0.504	1.067	0.177	1.377	1.058
LRRK2	0.416	1.002	0.168	1.341	0.141

In addition, we also ran Virtual Screening on a CNN model, using the BindingDB_IC50 dataset to obtain an IC50 binding score for Metformin and Simvastatin. The IC50 binding score for Simvastatin was 5.908941. The gene sources were referenced from NIH and genecards.org.

Lastly, we also ran Virtual Screening on broad anti-viral drug database to check for efficacy on SNCA the PD target of interest and below are the results of the scan (shown in **Table 4**).

Table 4. Anti-Viral Drug Virtual Scanning

Drug Name	Target Name	Binding Score
Fosamprenavir	SNCA	434.72
Darunavir	SNCA	1104.71
Lopinavir	SNCA	1221.13
Telaprevir	SNCA	1243.64
Nelfinavir	SNCA	1310.15
Peramivir	SNCA	1660.77
Daclatasvir	SNCA	1680.02
Simeprevir	SNCA	1870.44
Letermovir	SNCA	1913.70
Atazanavir	SNCA	1975.40
Saquinavir	SNCA	2197.46
Amprenavir	SNCA	2790.18
Raltegravir	SNCA	3397.50
Sofosbuvir	SNCA	3552.67
Rilpivirine	SNCA	4328.42
Vicriviroc	SNCA	5119.12
Arbidol	SNCA	5180.35
Dolutegravir	SNCA	5487.69
Elvitegravir	SNCA	5780.42
Tenofovir	SNCA	6404.55
Ritonavir	SNCA	7185.06
Amantadine	SNCA	7255.51
Abacavir	SNCA	8330.37
Enfuvirtide	SNCA	9327.03
Grazoprevir	SNCA	9655.95
Descovy	SNCA	9825.98
Podophyllotoxin	SNCA	11733.83
Adefovir	SNCA	11939.08
Chloroquine	SNCA	12128.78
Famciclovir	SNCA	12185.30

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None of these Anti-viral drugs above in the existing database seems to have a significant impact on PD and therefore were not considered for further exploration.

H. Molecular Interactions Analysis

To understand the molecular interaction of the selected targets, a String diagram [25, 26] was generated to study the five PD targets. **Figure 9** shows the interactions of these targets. The number of lines connecting any two targets indicates the strength of their interactions; the greater the number of lines, higher the strength of the interactions. From the String diagram we see that there are strong interactions between PRKN to PRK7/LRRK2/PINK1, LRRK2 to PINK1/SNCA, SNCA to PINK1(4 lines each) and a weak interaction between PARK7 to PINK1/LRRK2 (only 2 lines).

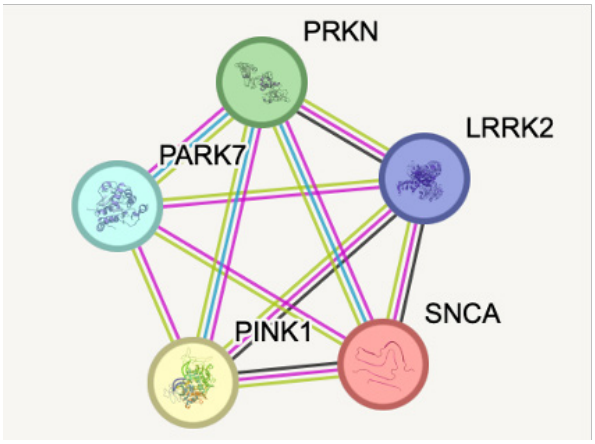

Figure 9. String diagram of the four compounds studied shows strength of interaction of the targets.

Table 5 shows the top 5 biological processes of the Gene Ontology (comprising of biological process (BP), molecular function (MF) and cellular component (CC) [25-28]. **Figure 10** shows the gene signal counts of various biological processes [28].

Table 5. Biological Process of gene ontology

Biological Process (Gene Ontology)	Strength	Signal
Dopamine Transport	3.02	5.14
Negative regulation of oxidative stress-induced neuron intrinsic ap..	3.37	4.26
Regulation of mitochondrial electron transport, NADH to ubiquinone	3.37	4.26
Regulation of synaptic vesicle transport	3.29	4.22
Dopamine uptake involved in synaptic transmission	3.29	4.22

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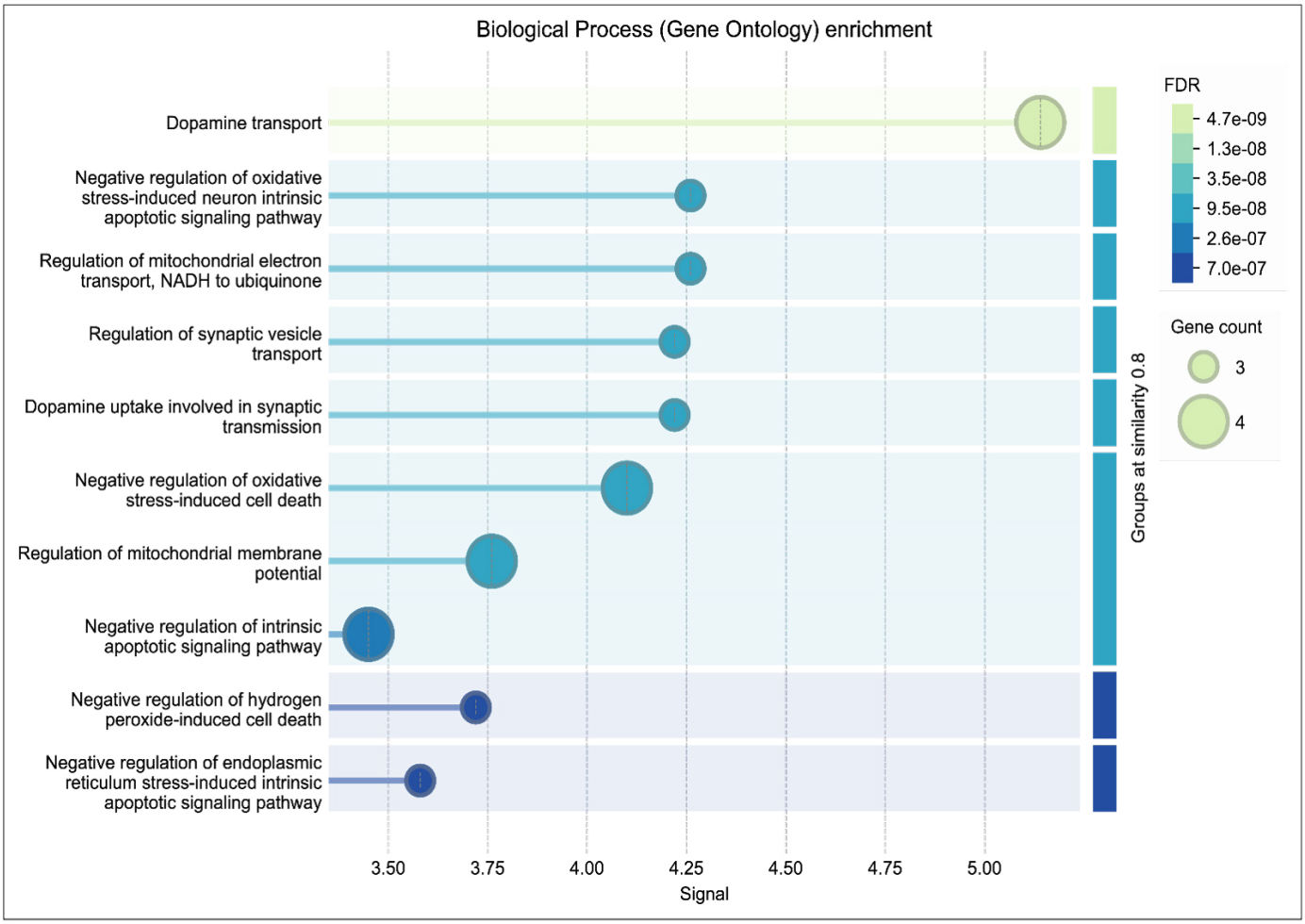

Figure 10. Biological Process and the Gene Signal Strength showing Dopamine transport has the strongest signal.

Dopamine transport is the strongest signal for the Gene Ontology and is as expected in PD since loss of dopamine producing neurons affects the dopamine transport.

I. Biological Filtering refs for each sentence

Metformin has some evidence of neuroprotection and reducing neuroinflammation, but the results are caveated due to moderate Blood-Brain Barrier (BBB) permeability [29]. Simvastatin has anti-inflammatory effects and good Central Nervous System (CNS) penetration and seems to have a strong result for PINK1 target [30]. Curcumin, although shows excellent results, has low absorption [31] and being a polyphenol that could sometimes show high binding scores due to it being a PAINS (pan-assay interference) compounds and an IMPs (invalid metabolic panaceas) candidate [32].

J. Multifactor Ranking

After applying various factors, such as binding strength, biological relevance, BBB/CNS impact scores, mechanism alignment, literature and safety [33], we analyzed the drugs based on these factors. The final score was calculated using:

Final Score=$\sum wi \cdot fi$,

where, Fi is a normalized factor, and wi is a weight. The most promising scores were for Remdesivir followed by Metformin and Simvastatin. Curcumin had good efficacy for being a natural polyphenol compound.

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CONCLUSIONS

Virtual Screening for drug repurposing could revitalize Parkinson's Disease treatment efforts and quickly bring about changes that may take longer using traditional approaches. In this study, we explored Virtual Screening with DeepPurpose, a powerful Python library for Drug-Target predictions (DTI) to identify which drugs provide the best binding scores.

Our results indicated that Metformin, Remdesivir, Simvastatin, and Curcumin had the best results, compared to the currently existing PD drug, Levodopa. The results for Levodopa were also included in the results for comparison.

The identified drugs showed strong scores for SNCA and PINK1 targets. SNCA is alpha-synuclein protein and is central to neuro toxicity [16]. PINK1 is a mitochondrial kinase enzyme, and if defective accumulates damaged mitochondria, causing oxidative stress and neuron damage [34].

Although the binding scores obtained look promising, it is imperative that they need further lab validation. DeepPurpose, a powerful Python-based tool used for rapid screening and Drug-Target predictions, has limitations, such as overfitting to training datasets and is reliant on the quality of SMILES strings. However, it offers a good starting point to help narrow down drugs that can be reviewed for their effectiveness on target sequences that have been identified. To transfer to clinical practice, further validation from in silico to in vitro analysis in a lab setting needs to be performed to confirm molecular binding.

FUNDING DECLARATION

No funding available

AUTHOR CONTRIBUTIONS

Conceptualization, K.V., R.S.; methodology, K.V.; software, K.V.; validation, K.V.; formal analysis, K.V., R.S.; investigation, K.V.; resources, K.V., R.S.; data curation, K.V.; writing—original draft preparation, K.V.; writing—review and editing, K.V.; visualization, K.V.; supervision, R.S.; project administration, R.S.; funding acquisition, R.S. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this publication can be made available upon request.

Vokkarne K, Sundararajan R. Drug Repurposing for Parkinson's Disease with Deep Learning: A Virtual Screening Approach. G Med Sci. 2026; 7(1):43-59. https://www.doi.org/10.46766/thegms.neuro.26010801

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