Exploration of Potential Drug Targets for Parkinson's via Text Mining and Data Analysis

Zihao Yang[1,#] and Sixian Wang[2,*]
[1]East China University of Political Science and Law,Shanghai 200042, China
[2]Department of Transfusion, Minhang Hospital, Fudan University, Shanghai 201199, China

Keywords: Text Mining, Differentially Expressed Genes (Degs), Genetic Diagnosis, Drug Discovery.

Abstract: Parkinson's disease (PD) is a chronic neurodegenerative disease of the central nerve system around the world. However, the current therapeutic regimens were not always effective. We found gene targets of existing drug and give indications of the potential value of new drugs by text mining and microarray data analysis. We firstly used text mining ("Parkinson's disease" and "parkinson") and microarray data analysis (GSE22491) to screen the genes that we want. Then, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis, as well as the protein-protein interaction (PPI) network were used to analysis the genes. Gene-drug interaction analysis was finally applied to the significant genes to provide insight into potential drug. As a result, we got 1,116 text mining genes (TMGs) and 4,437 differentially expressed genes (DEGs) through text mining and microarray data analysis. 258 genes were up-regulated genes and 31 genes were down regulated among the genes overlapped between TMGs and DEGs. There are six genes are significantand target 16 existing drugs. In summary, in this study, these six genes (Bax, Apaf-1, BCL2L11, Bcl-2, BCL2L1 and CYCS), associated with apoptosis, are the targets of 16 existing drugs. The finding may shed light on the indication of the drugs indications to Parkinson's disease.

1 INTRODUCTION

Parkinson's disease (PD) is a chronic neurodegenerative disease that affects the central nerve system and affects more than 6 million people worldwide. Among them, PD typically occurs in people over 60-year-old, with about 1% of the older suffering from the disease. Furthermore, males are more likely to suffer from PD than females (Scholpa et al. 2018). PD is less common in young adults under the age of 40, most cases are sporadic, and only around 10% are familial. Degeneration of dopamine (DA) neurons in the substantia nigra are one of the most common pathological features of PD, and the precise etiology of this pathological change remains unknown. Degeneration of dopamine neurons may be caused by genetic factors, aging, environmental factors, oxidative stress, and possibly other elements (Chen et al. 2017). Due to the slow progression of PD, the most obvious symptoms in the early phases are tremor, rigidity, bradykinesia and postural instability, and there may also be cognitive and behavioral problems. Although some treatments including medication, surgery and physical therapy have been used to relieve symptoms, such as dopamine receptor agonists and monoamine oxidase inhibitors to improve motor function, there is still no effective treatment for PD (Ganguly et al. 2018). Thus, there is an urgent need to discover new therapeutic drugs and effective strategies to effectively prevent the progression of PD to improve the therapeutic effect. In short, drugs that may be applied to prevent and treat PD can be obtained from text mining and data analysis strategies, providing new ideas for drug research and development and new applications.

In this study, we firstly used bioinformatics tools such as text mining and microarray data analysis to obtain common and unique genes. Significant differences between PD patients and control groups were depicted, while correlations between these

[a] https://orcid.org/0000-0002-0351-3501
[b] https://orcid.org/0000-0002-0777-3204

Yang, Z. and Wang, S.
Exploration of Potential Drug Targets for Parkinson's via Text Mining and Data Analysis.
DOI: 10.5220/0011231400003438
In *Proceedings of the 1st International Conference on Health Big Data and Intelligent Healthcare (ICHIH 2022)*, pages 83-91
ISBN: 978-989-758-596-8

genes existed. Secondly, these genes were screened for module genes and associated pathways using protein-protein interaction (PPI) network analysis. Finally, drug-gene interaction of module genes was performed in the drug gene interaction database (DGIdb), with the goal of discovering some current drugs to provide new ideas for the prevention and treatment of Parkinson's disease. Figure 1 depicts the framework of this study.

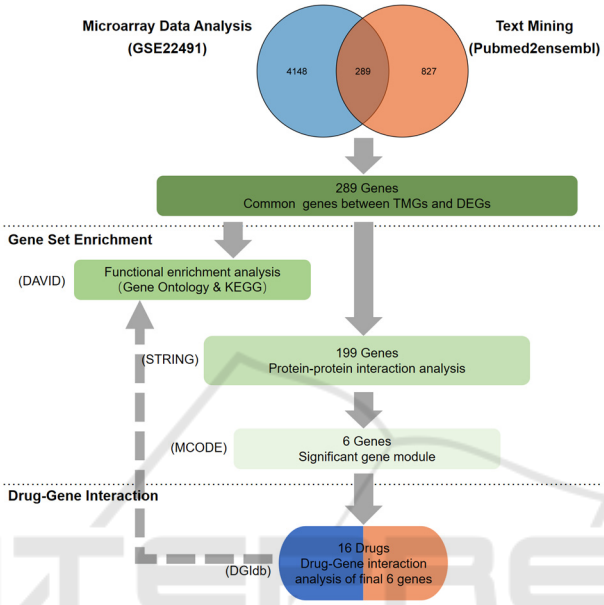


Figure 1: An overview of the workflow. Text mining for TMGs, Microarray data analysis for DEGs.

2 METHODS

2.1 Text Mining Analysis

We used GENCLIP3 (http://ci.smu.edu.cn/genclip3/analysis.php) to perform text mining. We entered the keyword, and the GENCLIP3 website can retrieve and extract all gene markers associated with the keyword from PubMed published articles (Wang et al. 2019). We entered the keyword "Parkinson's disease" and "parkinson" into GENCLIP3 and then extracted all non-repeat genes, and these gene sets formed the Text Mining Genes (TMGs).

2.2 Microarray Data Analysis

The microarray datasets of PD patients were searched from the publicly available GEO database (gene expression omnibus dataset). We screened the literature against inclusion and exclusion criteria and cross-checked it. Inclusion criteria: the approval of the Ethics Committee was indicated within the research; diagnosis of PD by clinical and neuropathology; raw microarray gene data can be obtained; raw GeneChip data had high quality. Exclusion criteria: the approval of the Ethics Committee was not indicated within the research; diagnosis of PD was not demonstrated by clinic and neuropathology; raw microarray gene data cannot be obtained; raw GeneChip data had poor quality. Following selection, GSE22491 files were obtained and downloaded.

GSE22491 expression files (.txt format files) and meta clinical information data (.soft format file) downloaded from GEO website, which was executed on the GPL6480 platform (Ron Edgar 2002, Barrett et al. 2009). The GSE22491 dataset comprises 18 blood samples from 10 Parkinson's disease (PD) patients and 8 healthy controls (Control) (Barrett et

al. 2007, Mutez et al. 2011). The probe identification numbers were converted into official gene symbols according to the annotation information of the GPL6480 platform. Afterwards, we counted duplicate genes, retained mRNA probes, deleted non-mRNA probes, and retained probes showing significant gene expression values for multiple probes of the same gene. Finally, we followed previous methods, and through manipulated the R language limma package to detect gene expression matrix, processed by Affy, AffyPLM packages, and obtain differentially expressed genes (DEGs) in Parkinson's disease samples and normal controls (Gautier et al. 2004, Larriba et al. 2019). As the threshold standards were utilized for the follow-up research, DEGs with the |log2 fold change (FC)| ≥1 and adjust P value <0.01, corrected by the Benjamini–Hochberg (BH) method (Wan et al. 2020). Crossing of DEGs and TMGs was then used as a starting point for further analysis.

2.3 Gene Ontology (GO) and KEGG Analysis of Overlapping genes

We adopted a research path similar to Zhao B et al., and briefly describe as follows (Zhao et al. 2020). Gene ontology (GO) is a common and useful note approach for annotating their functional features and gene products. Then, the GO terms were divided into three categories: biological process (BP), cellular component (CC), and molecular function (MF). The Kyoto Encyclopedia of Genes and Genomes (KEGG) is an open database resource for discovering biological functions and features of organic systems, especially in the datasets of gene chips and high-throughput experiments. (Kanehisa et al. 2017). Overlapping genes were analyzed by DAVID, a functional note bioinformatics microarray analysis website. Significance was assumed for $P < 0.05$.

2.4 Potential Protein-protein Interaction (PPI) Network Construction for Overlapping Genes

Potential protein-protein interaction of selected genes was generated using the STRING database (http://string-db.org) (Szklarczyk et al. 2019). As in a previous study by Wan Z et al., we also apply a similar principle (Wan et al. 2020). In this study, we used the STRING to construct the PPI network of overlapping genes, with a combined score > 0.4 considered statistically significant. We downloaded the TSV format file of protein-protein interaction (PPI), and PPI networks were created by Cytoscape software. Important gene modules (clusters) were classified by Molecular Complex Detection (MCODE) and STRING appin Cytoscape. These important gene modules are highly interconnected. Execute MCODE with default parameters. Drug-gene interaction analysis was applied to the genes in the gene module.

2.5 Drug-gene Interaction and Function Analysis of Potential Genes

To explore the possible application of new drug indications for the treatment of Parkinson's disease in humans, the drug gene interaction database (DGIdb) was handled to search for interactions between selected genes and existing drugs. The DGIdb database (http://www.dgidb.org) is an open access information website, which contains 41,102 genes, 14,449 drugs and 54,591 drug-gene interactions (Freshour et al. 2021). In the present study, we used the DGIdb database to search and filter information on the interactions between selected genes and existing drugs, screen potential matches with these drugs, and carry out functional enrichment analysis (Zhao et al. 2020).

2.6 Statistics Analysis

According to the experience of many academic circles(Kirk et al. 2018, Pan et al. 2018, Zhang et al. 2019, Wan et al. 2020, Zhao et al. 2020, Zhao et al. 2020), we used a moderated t-test to identify DEGs. We used fisher's Exact Test to analyzed GO and KEGG annotation enrichments (Fisher 1922). All statistical analysis was performed with the R version 3.5.3 software.

3 RESULTS

3.1 Screening of TMGs and DEGs

As shown in Figure 1, We got 1,116 TMGs and 4,437 DEGs through text mining and microarray data analysis. As shown in Table I, there were 289 overlapping genes between TMGs and DEGs, and 258 genes were up-regulated and 31 genes were down-regulated.

Table 1: The 289 overlapped genes between TMGs and DEGs.

Overlapped genes	*Gene Symbol*
Up-regulated genes	*DYRK1A,PPP3CA,SKP1,EP300,TAF9,DLD,HBB,*CYCS,UBE2K,YWHAE,NDUFS1,HMGB1,HPRT1,GLUL,AIFM1,SMS,CLINT1,TCP1,HSPA9,MTHFR,REL,CARD8,OPA1,GLO1,FBXO7,MTR,NDUFA5,GSTO1,SON,GTF2I,YWHAZ,CDC42,CREB1,ATF6,ITM2B,UCHL3,ATG5,DR1,CHMP2B,DECR1,ADRBK2,FMR1,RAN,MUTED,BNIP3L,MAP2K3,UBE2L3,ALDH2,TFAM,BCL10,PDCD2,PARK7,DNM1L,PPM1A,FECH,PDHB,EGLN1,PDP1,RBX1,MAP2K4,APPL1,PTEN,GSK3B,TXN,SSR1,SFPQ,SLC2A1,FAS,MEF2A,MXI1,ARPP19,SERPINI1,YY1,NUCB2,DEK,TP53INP1,BAG5,MAPK14,YWHAQ,C1orf9,LARS,FKBP1A,ZCRB1,MYO5A,ABHD5,PANK2,PCNA,ARHGDIB,NEDD8,TAF1,GCLC,CD55,RB1,NOC2L,IRF2,BCKDHB,FLOT1,RNF41,DPYSL2,ABAT,USP24,MTIF3,SRI,GLB1,*BCL2L11,LAMP2,GTPBP4,POLG,PSMC1,GNE,AGPS,PDIA3,MAP3K5,PSMD9,ANXA1,ASPSCR1,DLG4,ATXN3,NDUFB6,UBE2A,HSD17B4,TFCP2,CNDP2,*APAF1,MSN,PGK1,CBS,MTFMT,AOC3,MAPK1,*BCL2L1,KIAA1267,FXN,TUBB,GNPTAB,HSPA4,GPI,GLUD1,UBB,HSPA8,MEA1,PSMA6,EIF2AK2,PPP4C,EIF2AK3,DPYD,BCL2L2,B2M,BAP1,LMNA,S100A6,HSP90AB1,TARDBP,HSF1,MRPS7,MAP3K7,SMG1,FOXO4,MBP,LIAS,GCH1,LPP,FANCB,SHMT1,TFB2M,IKBKAP,MDM2,SSNA1,PRRG4,NDUFS4,EIF2C2,MTSS1,SNCA,IMMT,RTN4,ACTB,COPS2,AHR,HSPA5,PRKAA1,YWHAH,SMN2,ADCY7,ACO2,HSPD1,PTPRC,CAST,RAF1,GSN,PAWR,SLC6A8,NMT1,PAF1,PPP3CC,HNMT,TBP,LIMS1,UPP1,NONO,CTNNBL1,HSPA1A,PES1,LMOD1,IQCB1,HDAC9,PDLIM7,CHM,VIM,TOR1B,UBR5,ATP1A3,HIF1A,BRCA1,SDPR,SMARCB1,TSPO,AGFG1,ERGIC2,DHDDS,CSNK2A1,TKT,CD44,PARP1,GALC,RAI1,GALNS,PDPK1,TUBA1A,MAP3K1,CASP1,ENO1,UROD,PPARA,KIF11,MAP2K1,CANX,RB1CC1,TNFRSF1A,FES,IGF2R,DLX4,UCHL1,GATA1,KIAA0101,HLAE,TUBB3,AES,CA1,PTPN11,IDE,SOD1,PON2,ITGAM,PINK1,ANXA5,NOD2,HLA-A,HLA-B*
Down-regulated genes	*BEST1,SOX1,FHIT,PRNP,CKB,TPSG1,THY1,GRIN1,EN2,SYN1,ZFPM1,TH,*BCL2,CD4,GDNF,BBC3,SLC17A7,AVP,CHRNA4,ATN1,FGF3,*BAX,DRD4,ALDOA,ACAP3,TBX1,OXT,DRD2,GGT1,MYC,GFRA3*

*, the final six genes

3.2 GO and Pathway Enrichment Analysis

To better understand the functions of overlapping genes, GO and KEGG pathway enrichment analyses were analyzed using an online tool DAVID. Figure 2 showed that the top six significant enrichment terms for biological process (BP), cellular component (CC), molecular function (MF) and KEGG of overlapping genes. In BP annotation, it was significantly involved in the cell death, apoptotic process, and regulation of programmed cell death, which are all related to neuronal cell death as the major event in PD. In the CC category, it was mainly involved in the cytosol, mitochondrion, myelin sheath. In the MF category, genes were primarily enriched in “ubiquitin-like protein ligase binding”, “enzyme binding” and “protein kinase binding”. KEGG analysis showed that the overlapping genes were mainly involved in Alzheimer's disease, Parkinson's disease and apoptosis.

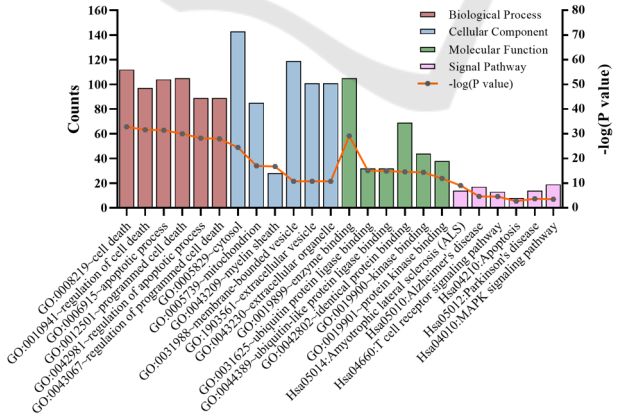
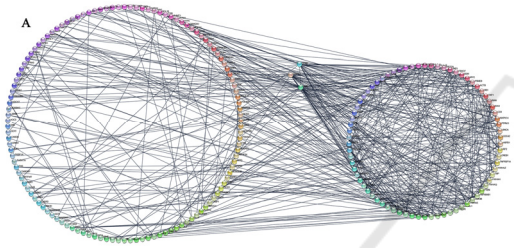


Figure 2. The top six significant GO terms and KEGG pathways of common genes. The bar charts represent the counts of genes classified in the BP, CC, MF and KEGG respectively; the yellow line chart represents the significance of enrichment terms. GO, gene ontology; BP, biological process; CC, cellular component; MF, molecular function; KEGG, Kyoto Encyclopedia of Genes and Genomes.

3.3 Protein Interaction and Module Analysis

The 289 overlapping genes were entered into the STRING database and then statistically analyzed using the STRING APP within Cytoscape software. The results are shown in Figure 3A. A total of 199 genes/nodes with 556 edges participated in the construction of the PPI networks, and 5 genes haven't fallen into the PPI networks. The 6 significant genes were screened as potential targets for drug-gene interaction analysis using MCODE application built in Cytoscape software. The significant gene module consists 6 genes/nodes with 13 edges/interactions, which exhibit 4 up-regulated genes (*CYCS, BCL2L11, APAF1 and BCL2L1*) and 2 down-regulated genes (*BCL2, BAX*) (*Fig. 3B*).



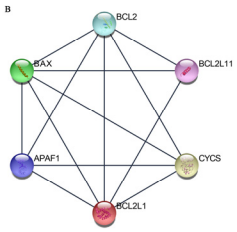
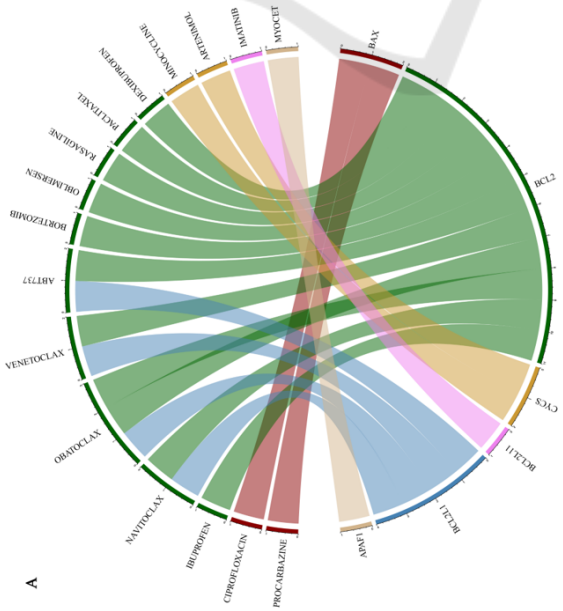


Figure 3. The PPI networks construction and significant gene module analysis. (A) The entire PPI networks of common genes. (B) The significant gene module, including 6 genes.

3.4 Drug-gene Interaction and Functional Analysis

The 6 genes clustered in the significant gene module were eventually screened as potential targets for drug-gene interaction analysis using MCODE application built in Cytoscape software. Six key genes target to 16 drugs. It was divided into 7 types, with their drug indications (*Figure 4A, Table II*). Furthermore, as shown in Figure 4B, the six target genes are mainly involved in the intrinsic apoptotic signaling pathway, the positive regulation of the apoptotic process and the positive regulation of programmed cell death. In the CC category, it was mainly involved in the Bcl-2 family protein complex, mitochondrial outer membrane, organelle outer membrane. In the MF category, genes were primarily enriched in "BH3 domain binding", "death domain binding" and "BH domain binding".



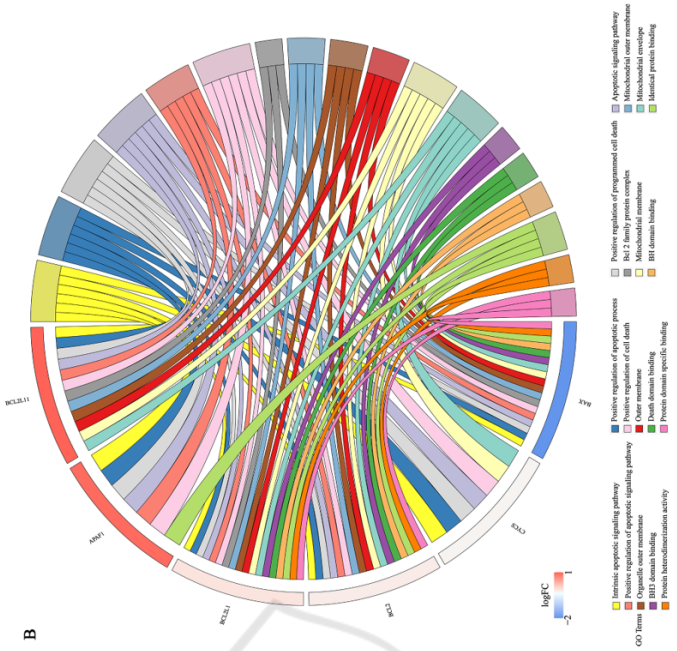


Figure 4. The drugs targeted to genes and its functional enrichment analysis. (A) Chord plot for the connection between 6 drugs and 16 genes. (B) Chord plot for functional enrichments of 6 genes.

Table 2: The specified information of drugs and its target genes.

Number	Gene	Drug	Interaction	Drug class*
1	BCL2	IBUPROFEN	Modulator	Anti-inflammatory agents, nephrotoxic agents, other nonsteroidal anti-inflammatory agents, causing angioedema agents, causing hyperkalemia agents, produce hypertension agents
2	BCL2	NAVITOCLAX	Antagonist,Inhibitor	Anti-inflammatory agents
3	BCL2	OBATOCLAX	Inhibitor	Antineoplastic agent
4	BCL2	VENETOCLAX	Antagonist,Inhibitor	Antineoplastic agent, apoptosis regulator Bcl-2 inhibitor,antineoplastic and immunomodulating agents
5	BCL2	ABT 737	Antagonist	Not available
6	BCL2	BORTEZOMIB	Inhibitor	Antineoplastic agent,cardiotoxic antineoplastic
7	BCL2	OBLIMERSEN	Antisense oligonucleotide	agents,hepatotoxic agents,immunosuppressive agents,potential qtc-prolonging agents
8	BCL2	OBATOCLAX	Inhibitor	Antineoplastic agent
9	BCL2	RASAGILINE	Activator	Not available
10	BCL2	PACLITAXEL	Inhibitor	Antiparkinson agent,antidepressive agents, serotonin agents
11	BCL2	DEXIBUPROFEN	Inhibitor,negative modulator	Antineoplastic agent,antiinflammatory agent,causing
12	BCL2L1	ABT 737	Antagonist	muscle toxicity agents,cardiotoxic antineoplastic agents,neurotoxic agents
13	BCL2L1	NAVITOCLAX	Antagonist,Inhibitor	Anti-inflammatory agents,nephrotoxic agents
14	BCL2L1	OBATOCLAX	Inhibitor	Not available

15	BCL2L1	VENETOCLAX	Antagonist	Antineoplastic agent, apoptosis regulator Bcl-2 inhibitor,antineoplastic and immunomodulating agents
16	CYCS	MINOCYCLINE	Inhibitor,negative modulator	Photosensitizing agents,causing muscle toxicity agents
17	CYCS	ARTENIMOL	Ligand	Antiparasitic agents,anti-infective agents
18	BCL2L11	IMATINIB	Inhibitor	Antineoplastic agent,antineoplastic agents,cardiotoxic antineoplastic agents,qtc prolonging agents,photosensitizing agents
19	APAF1	MYOCET	Inhibitor	Not available
20	BAX	PROCARBAZINE	Inhibitor	Antineoplastic agent, antidepressive agents,serotonin agents
21	BAX	CIPROFLOXACIN	Inhibitor	Antineoplastic agent,photosensitizing agents,qtc prolonging agents

*, the drug indications have been approved by FDA

4 DISCUSSION

Parkinson's disease is a common neurodegenerative disorder caused by the degeneration and apoptosis of dopaminergic neurons. In this study, the aim was to find potential therapeutic drugs for PD based on text mining and data analysis, and to provide fresh ideas for research into new applications of conventional drugs. As shown in Figure 4, we finally identified 6 potential genes and 16 existing drugs for PD, which could be utilized as targets and drugs for the study of PD.

Based on a search of the published literature, we found these six genes are tightly associated with PD. Four genes (*Bax, Apaf-1, BCL2L11* and *CYCS*) show a promotive effect, while the other two (*Bcl-2* and *BCL2L1*) sustain an inhibitory effect on PD. The family of Bcl includes the anti-apoptosis genes (*Bcl-2, Bcl-xL,* etc.) and the pro-apoptosis genes (*Bax, BCL2L11,* etc.). It inhibits or promotes the release of cytochrome C (*CYCS*) into the cytoplasm, which binds to Apaf-1 (*apoptosis protease activating factor-1*) , thus induces apoptosis. This process is involved in the degeneration and apoptosis of dopaminergic neurons in PD (Xu et al. 2007, Liu et al. 2020). According to Wolter et al., BCL2-Associated X (*Bax*) is the main pro-apoptotic gene in the Bcl-2 gene family(Reljic et al. 2016). Under normal conditions, Bax is present as a monomer in the outer mitochondrial membrane or cytoplasm, but upon induction of apoptosis, Bax is specifically translocated to the mitochondria.

The B-cell lymphoma-2 (*Bcl-2*), an important anti-apoptosis gene, is correlated with cell apoptosis. In general, the Bcl-2 and Bax genes regulate apoptosis, and Bcl-2 binds to Bax, further inhibiting Bax and promoting cell survival (Wolter et al. 1997). CYCS encodes a protein that binds to the inner membrane of mitochondria, where it receives electrons from cytochrome B and transfers them to the cytochrome oxidase complex, thus participating in the initiation of apoptosis (Reljic et al. 2016). It is well known that CYCS release, activation of cellular caspases and subsequent apoptosis are thought to be among the important factors leading to neuronal cell death (Lederer et al. 2007). Reljic et al. elucidated that BCL2L1 belongs to the Bcl-2 protein family of anti-apoptotic or pro-apoptotic regulators (Nicosia et al. 2020). The protein encoded by this gene contains a BCL-2 homologous structural domain 3 (*BH3*). Its interaction with other members of the BCL-2 protein family and role as an apoptotic activator is verified. Chen, et al. clarified that the BCL2-like protein 1 (*BCL2L1*) gene encodes a mitochondrial protein thought to prevent apoptosis in normal cells (Chen et al. 2019). BCL2L1 may regulate the opening of channels in the outer mitochondrial membrane and control the release of cytochrome c. Apaf-1 is a key molecule in the intrinsic pathway of apoptosis (Nicosia et al. 2020).

As evidenced by numerous literatures, the main characteristic of PD is the degeneration and death of dopaminergic neurons in the midbrain. Apoptosis, also known as programmed cell death, is one of the key mechanisms leading to degeneration and death of dopaminergic neurons in PD patients (Xu et al. 2007, Wilczynski et al. 2017, Liu et al. 2020). The extrinsic and the intrinsic apoptosis pathway are the two main signaling pathways for apoptosis. The extrinsic apoptosis pathway is activated in PD pathology, but the underlying mechanisms are yet to be further investigatied (Mao et al. 2016, Zhang et al. 2020). The mitochondrial mediated cell apoptosis intrinsic pathway is stimulated by positive factors (eg. toxins, radiation and hypoxia) or negative factors (eg. the absence of hormones and growth factors in the cell)

Pro-apoptotic genes such as BAX are then up-regulated, while anti-apoptotic genes such as BCL-2 and BCL2L1 are repressed. This arouses change in the permeability of mitochondrial cell membrane, resulting in the opening of the mitochondrial permeability transition pore (*mPTP*) (Wang et al. 2020). Pro-apoptotic proteins such as cytochrome C are released from the mitochondria into the cytosol and bind to Apaf-1 to form apoptosomes, which activate the caspase cascade. In particular, the apoptosome activates caspase-9, which in turn activates caspase-3 and other downstream caspases, leading to apoptosis (Xu et al. 2007).

The drug interactions between the 6 genes within 16 existing drugs we identified can be divided into four types, namely modulator, agonist, binder, antagonist and inhibitor (*Table II*). These drugs can be classified into several categories, including anti-parkinson agents, anti-inflammatory agents, anti-depressive agents, immunomodulating and anti-neoplastic agents. The types of drugs identified in this study were broader and more focused on addressing PD symptoms that may be caused by apoptotic factors than those as potential treatments for PD in previous literature (Xu et al. 2018, Raasmaja et al. 2019, Elbeddini et al. 2020). The combined use of drugs may have synergistic therapeutic effects, for example reducing side effects and improving selectivity. While these existing drugs offer a new perspective on the study of PD, their new functions and indications need to be confirmed in further clinical trials.

5 CONCLUSIONS

According to the text mining conception (keyword: Parkinson's disease and parkinson) and microarray data analysis (dataset: GSE22491), we found 16 existing drugs, approved by FDA, target to six genes, which involved in the intrinsic apoptotic signaling pathway. These genes might be used for Parkinson's disease, as well as its original drug indications.

ACKNOWLEDEGMENTS

Thanks to Zhao’s Team of Xiamen University for suggestions on the manuscript.

REFERENCES

Barrett, T., et al. (2007). "NCBI GEO: mining tens of millions of expression profiles--database and tools update." Nucleic Acids Res **35**(Database issue): D760-765.

Barrett, T., et al. (2009). "NCBI GEO: archive for high-throughput functional genomic data." Nucleic Acids Res **37**(Database issue): D885-890.

Chen, C., et al. (2019). "Role of long non-coding RNA TP73-AS1 in cancer." **39**(10).

Chen, Y., et al. (2017). "The expression and significance of tyrosine hydroxylase in the brain tissue of Parkinsons disease rats." Exp Ther Med **14**(5): 4813-4816.

Elbeddini, A., et al. (2020). "Potential impact and challenges associated with Parkinson's disease patient care amidst the COVID-19 global pandemic." J Clin Mov Disord **7**: 7.

Fisher, R. A. (1922). "On the Interpretation of χ² from Contingency Tables, and the Calculation of P." Journal of the Royal Statistical Society **85**(1): 87-94.

Freshour, S. L., et al. (2021). "Integration of the Drug–Gene Interaction Database (DGIdb 4.0) with open crowdsource efforts." Nucleic Acids Research **49**(D1): D1144-D1151.

Ganguly, U., et al. (2018). "Alpha-synuclein, Proteotoxicity and Parkinson's Disease: Search for Neuroprotective Therapy." Curr Neuropharmacol **16**(7): 1086-1097.

Gautier, L., et al. (2004). "affy--analysis of Affymetrix GeneChip data at the probe level." Bioinformatics **20**(3): 307-315.

Kanehisa, M., et al. (2017). "KEGG: new perspectives on genomes, pathways, diseases and drugs." Nucleic Acids Res **45**(D1): D353-D361.

Kirk, J., et al. (2018). "Text mining-based in silico drug discovery in oral mucositis caused by high-dose cancer therapy." Support Care Cancer **26**(8): 2695-2705.

Larriba, Y., et al. (2019). Microarray Data Normalization and Robust Detection of Rhythmic Features. Microarray Bioinformatics**:** 207-225.

Lederer, C. W., et al. (2007). "Pathways and genes differentially expressed in the motor cortex of patients with sporadic amyotrophic lateral sclerosis." BMC Genomics **8**: 26.

Liu, Y., et al. (2020). "Preparation and Neuroprotective Activity of Glucuronomannan Oligosaccharides in an MPTP-Induced Parkinson's Model." Mar Drugs **18**(9).

Mao, Y., et al. (2016). "Regulation of cell apoptosis and proliferation in pancreatic cancer through PI3K/Akt pathway via Polo-like kinase 1." **36**(1): 49-56.

Mutez, E., et al. (2011). "Transcriptional profile of Parkinson blood mononuclear cells with LRRK2 mutation." Neurobiol Aging **32**(10): 1839-1848.

Nicosia, A., et al. (2020). "Carbon Nanodots for On Demand Chemophotothermal Therapy Combination to Elicit Necroptosis: Overcoming Apoptosis Resistance in Breast Cancer Cell Lines." Cancers (Basel) **12**(11).

Pan, Y., et al. (2018). "Text miningbased drug discovery in cutaneous squamous cell carcinoma." Oncol Rep **40**(6): 3830-3842.

Raasmaja, A., et al. (2019). "The Water Extract of Juniperus communis L. Induces Cell Death and Sensitizes Cancer Cells to Cytostatic Drugs through p53 and PI3K/Akt Pathways." Int J Mol Sci **20**(9).

Reljic, B., et al. (2016). "BAX-BAK1-independent LC3B lipidation by BH3 mimetics is unrelated to BH3 mimetic activity and has only minimal effects on autophagic flux." Autophagy **12**(7): 1083-1093.

Ron Edgar, M. D. a. A. E. L. (2002). "Gene Expression Omnibus: NCBI gene expression and hybridization array data repository." Published by Oxford University Press **Nucleic Acids Research, 2002, Vol. 30, No. 1 207–210**.

Scholpa, N. E., et al. (2018). "5-HT1Freceptor-mediated mitochondrial biogenesis for the treatment of Parkinson's disease." British Journal of Pharmacology **175**(2): 348-358.

Szklarczyk, D., et al. (2019). "STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets." Nucleic Acids Res **47**(D1): D607-D613.

Wan, Z., et al. (2020). "Drug discovery in cardiovascular disease identified by text mining and data analysis." Ann Palliat Med **9**(5): 3089-3099.

Wang, J. H., et al. (2019). "GenCLiP 3: mining human genes' functions and regulatory networks from PubMed based on co-occurrences and natural language processing." Bioinformatics.

Wang, Y., et al. (2020). "Ma xing shi gan decoction eliminates PM2.5-induced lung injury by reducing pulmonary cell apoptosis through Akt/mTOR/p70S6K pathway in rats." Biosci Rep **40**(7).

Wilczynski, J., et al. (2017). "Body Posture, Postural Stability, and Metabolic Age in Patients with Parkinson's Disease." Biomed Res Int **2017**: 3975417.

Wolter, K., et al. (1997). "Movement of Bax from the cytosol to mitochondria during apoptosis." **139**(5): 1281-1292.

Xu, C., et al. (2018). "Potential Therapeutic Drugs for Parkinson's Disease Based on Data Mining and Bioinformatics Analysis." Parkinsons Dis **2018**: 3464578.

Xu, J., et al. (2007). "Rifampicin protects PC12 cells against MPP+-induced apoptosis and inhibits the expression of an alpha-Synuclein multimer." Brain Res **1139**: 220-225.

Zhang, N., et al. (2019). "Computational Drug Discovery in Chemotherapy-induced Alopecia via Text Mining and Biomedical Databases." Clin Ther **41**(5): 972-980 e978.

Zhang, Y., et al. (2020). "Small molecule CDS-3078 induces G2/M phase arrest and mitochondria-mediated apoptosis in HeLa cells." Exp Ther Med **20**(6): 284.

Zhao, B., et al. (2020). "Comprehensive analysis reveals a six-gene signature and associated drugs in mimic inguinal hernia model." Hernia **24**(6): 1211-1219.

Zhao, B., et al. (2020). "Six-Gene Signature Associated with Immune Cells in the Progression of Atherosclerosis Discovered by Comprehensive Bioinformatics Analyses." Cardiovasc Ther **2020**: 1230513.