Intrinsic Mechanism of Anticancer Drugs in Neurodegenerative Disorders

THESIS

Submitted to the Delhi Technological University for the award of the degree of

DOCTOR OF PHILOSOPHY

Submitted by

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Dedicated to
My Mother

DECLARATION

I hereby declare that the thesis entitled **"Intrinsic mechanism of anticancer drugs in neurodegenerative disorders"** submitted by me, for the award of the degree of ***Doctor of Philosophy*** to **Delhi Technological University (Formerly DCE)** is a record of *bona fide* workcarried out by me under the guidance of Prof. Pravir Kumar.

I further declare that the work reported in this thesis has not been submitted and will not be submitted, either in part or in full, for the award of any other degree or diploma in this Instituteor any other Institute or University.

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CERTIFICATE

This is to certify that the thesis entitled **"Intrinsic mechanism of anticancer drugs in neurodegenerative disorders"** submitted by **Ms. Dia Advani** to **Delhi Technological University (Formerly DCE)**, for the award of the degree of "Doctor of Philosophy" in Biotechnology is a record of *bona fide* work carried out by him. Dia Advani has worked under my guidance and supervision and has fulfilled the requirements for the submission of this thesis, which to our knowledge has reached requisite standards.

The results contained in this thesis are original and have not been submitted to any other university or institute for the award of any degree or diploma.

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ABSTRACT

As the global population is growing progressively older, the prevalence of life-threatening neurodegenerative disorders is increasing. The mechanism and pathologies of these disorders are still undecipherable and only disease-modifying treatments are available. Drug therapy is crucial for treating serious neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. The immediate need for exploring novel treatment options calls for designing efficacious drug development strategies. In the recent past, there has been a growing interest in drug repurposing for incurable diseases. Drug repurposing offers an accelerated pathway for using existing drugs for novel indications with remarkable reduction in drug development time and cost. Advancements in screening technologies and the discovery of data-driven repurposing strategies have expedited the repurposing process for various diseases. In the context of neurodegenerative disorders, anticancer drugs are gaining immense attention and various drugs have been tested in different neurodegenerative disorders. Currently, various computational methods, including molecular, structural and clinical methods, present great opportunities to investigate repurposed drugs for neurodegenerative disorders. However, the heterogeneous disease states, lack of effective validation methods and experimental obstacles oppose the process of drug development. Therefore, we identified the problem of lack of efficacious methods to facilitate drug repurposing for various neurodegenerative disorders, specifically Alzheimer's disease and Parkinson's disease.

Here, the main objective of this Ph.D. work is to understand the biological rationale for repurposing anticancer drugs for neurodegenerative disorders. We investigated the common molecular mechanism of Alzheimer's disease, Parkinson's disease and cancer. We opted an integrated approach including genomics, transcriptomics and proteomics data to unravel the

common molecular signatures. Further, we extensively analyzed the overlapping pathways, biological processes and regulatory signatures such as transcription factors and micro RNAs. We explored various FDA-approved anticancer drugs and validated their repurposing potential as neuroprotectants by applying different computational methods such as structural similarities, Cmap analysis, molecular docking and simulations. To further extend our research, we also explored the repurposing aspects of natural anticancer compounds for some common targets against Alzheimer's and Parkinson's diseases.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF GRAPHS

ABBREVIATIONS

Abbreviation	Definition
ABCA1	ATP-binding cassette transporter 1
ABCG1	ATP binding cassette sub-family G member 1
ABL1	ABL proto-oncogene
ADME	Absorption, distribution, metabolism, excretion
AChE	Acetylcholinesterase
AD	Alzheimer's disease
AIMP-2	Aminoacyl-tRNA synthetase complex-interacting multifunctional protein 2
ALS	Amyotrophic lateral sclerosis
AMPPNP	Phosphoaminophosphonic acid-adenylate ester
APL	Acute Promyelocytic Leukemia
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
Aβ	Amyloid-beta
BACE1	Beta secretase 1
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
bFGF	Basic fibroblast growth factor
BRCA	Breast cancer
CAS	Catalytic anion site
CDKs	Cyclin-dependent kinases
CINV	Chemotherapy-induced nausea and vomiting
CIPN	Chemotherapy-induced peripheral neuropathy
Cmap	Connectivity map
CNS	Central nervous system
CoDReS	Computational drug repurposing score
CSF	Cerebrospinal fluid
CYC	Cyclophosphamide
DILI	Drug-induced liver injury
DJ1	Protein deglycase
EAE	Experimental Autoimmune Encephalomyelitis
EGFR	Epidermal growth factor receptor
ERBB4	Erb-b2 receptor tyrosine kinase 4
ERK	Extracellular signal regulated kinase
FAD	Flavin adenine dinucleotide
FLT1	Fms related receptor tyrosine kinase 1
FYN	Fyn proto-oncogene
GREIN	GEO RNA-seq Experiments Interactive Navigator
GS2D	Gene set to Diseases
GSH	Glutathione
GSH/GSSG	Reduced/oxidized glutathione
GSK3B	Glycogen synthase kinase beta

H_2S	Hydrogen sulfide
HD	Huntington's disease
HMDB	Human Metabolome Database
HMDD	Human microRNA Disease Database
IL-1β	Interleukin-1 beta
iLINCS	Integrative LINCS
JNK	c-Jun N-terminal kinase
KDR	Kinase insert domain receptor
LRRK2	Leucine rich repeat kinase 2
LXR	Liver X receptor
mAb	Monoclonal antibody
MAO	Monoamine oxidases
MAPKs	Mitogen-activated protein kinases
MAPT	Microtubule-associated protein tau
MCS	Maximum common substructure
MDM2	Mouse double minute 2 homolog
mHtt	Mutant huntingtin
MIST	Molecular Interaction Search Tool
MM-PBSA	Molecular Mechanics Poisson-Boltzmann surface area
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRP	Multidrug-resistant proteins
MS	Multiple sclerosis
NDDs	Neurodegenerative
NIH	National Institutes of Health
NME	New molecular entities
NO	Nitric oxide
PD	Parkinson's disease
PDB	Protein data bank
Pgp	P glycoprotein
PI3K-PKB/Akt	Phosphoinositide-3-kinase-protein kinase B/Akt
PINK1	PTEN-induced kinase 1
PPARγ	Peroxisome proliferator-activated receptor gamma
PS	Presenilin
QSAR	Quantitative structure-activity relationship
Rg	Radius of gyration
RMSD	Root mean square deviation
RMSF	Root mean square fluctuation
ROS	Reactive oxygen species
RRMS	Relapsing-remitting MS
RT-PCR	Reverse transcriptase-polymerase chain reaction
RXR	Retinoid X Receptor
SNCA	Synuclein alpha
SNP	Single nucleotide polymorphism
SOD1	Superoxide dismutase

SPCE	Simple point charge
SRC	Src proto-oncogene
TGFβ	Transforming growth factor-beta
TNFα	Tumor necrosis factor-alpha
TPSA	Topological polar surface area
TTD	Therapeutic Target Database
UniProtKB	UniProt Knowledgebase
UPR	Unfolded protein response
UPS	Ubiquitin proteasome system
VEGF	Vascular endothelial growth factor
Wnt	Wingless-type murine-mammary tumor virus integration site
WHO	World Health Organization

CHAPTER I

INTRODUCTION

CHAPTER I: INTRODUCTION

1.1 OVERVIEW

Neurodegenerative (NDDs) disorders are one of the most alarming medical illnesses affecting the brain and nervous system. The Lack of understanding of the disease-leading mechanisms makes the treatment options unavailable. Currently, an estimated 35.6 million people are surviving with Dementia, and the number is presumed to triple by the next 30 years [1]. According to the report of the World Health Organization (WHO), in the next 20 years, NDDs affecting motor functions will be the second most widespread reason for human death [2]. NDDs are categorized based on clinical features- dementia, parkinsonism, or motor neuron disease, or based on the anatomic areas covered- spinocerebellar degeneration, frontotemporal degeneration and extrapyramidal disorders. In general, amyloidoses, tauopathies, α-synucleinopathies, and TDP-43 proteinopathies are the most widespread NDDs. Abnormal protein aggregation is the major hallmark feature of all NDDs associated with some fundamental processes such as progressive neuronal loss, neuroinflammation, dysfunction of the Ubiquitin proteasome system (UPS), abnormal autophagic processes, oxidative insult, and neuronal apoptosis [3]. Alzheimer's disease (AD), Parkinson's disease, Amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and Multiple sclerosis (MS) are the major NDDs affecting the global health.

Aging is the biggest risk factor for various diseases, from cancer to NDDs. These age-related diseases can be categorized into two groups. Loss-of-function diseases like NDDs are represented by the loss of cells, tissues, or optimal physiological functions. While gain-of-function diseases like cancer exhibit gain of cells and, sometimes, new cellular functions [4]. Several biological and pathological mechanisms confirm the connection between

neurodegeneration and oncogenesis. The interesting connection between cancer and neurodegeneration opens up new possibilities for the repurposing of oncology drugs for neuroprotection. Many are already in clinical trials, and some are in experimental phases. Drug repurposing, drug reprofiling, or drug repositioning is a productive method to use already approved drugs for a different condition but with some common mechanism of action. This approach has been successful in many conditions like cardiovascular diseases, obesity, Parkinson's disease, cancer, irritable bowel syndrome, and psychosis [5]. The main advantage of drug repositioning is that the pharmacokinetic properties and toxicology of the candidate drugs have already been established. This hastens the process of drug development and reduces cost factors.

1.2 RATIONALE OF THE STUDY

- Cancer and neurodegeneration share an intricate yet overlapping genetic and molecular mechanisms.
- Current available therapeutics for AD and PD are providing symptomatic treatment and give an ultimatum for developing new therapeutic strategies.
- Experimental and clinical studies have validated the concept of repurposing anticancer drugs for NDDs.
- Drug repurposing is an efficient and rapid strategy of drug development with less time and money expenditure.
- Natural compounds serve significant opportunities for drug repurposing for NDDs.

1.3 AIMS AND OBJECTIVES

1.3.1 AIMS

Drug repurposing and signaling mechanism elucidation of anticancer drugs in neurodegenerative disorders

1.3.2 OBJECTIVE

1. To investigate the common molecular mechanisms between neurodegenerative disorders and cancer based on multi-omics approach.
2. To repurpose anticancer drugs for neurodegenerative disorders and study their signaling mechanisms.
3. To identify the repurposing potential of anticancer natural compounds as neuroprotective agents.

1.4 SUMMARY OF THESIS

The present Ph.D. thesis is organized into seven different chapters. Chapter 1 provides a background knowledge of the study, rationale of the study, and the research aim and objectives. Chapter 2 gives a compendium of the available studies related to the topic of the research. The overlapping mechanisms of different NDDs and cancer are described in detail. The main focus of the chapter is to highlight the concept of drug repurposing with associated advantages and challenges. Additionally, the clinical and experimental studies of anticancer repurposed drugs in the five major NDDs, including AD, PD, HD, ALS and MS are discussed. Further, the chapter highlights the repurposed anticancer drugs identified for various NDDs.. Chapter 3 includes the integrated multi-omics (genomics, transcriptomics and proteomics) analysis of AD and PD data and its interactive overlap with cancer genes.

Further, it shows the repurposing potential of anticancer drugs for AD and PD confirmed by different filters applied. The chapter proposes the possible mechanisms of the identified repurposed drugs. Chapter 4 of the thesis explores the interconnection of PD and breast cancer (BRCA). The data collection was done by three different omic layers and the resultant common genes were used to identify common regulatory molecules, biological pathways, cellular processes and drugs. We also investigated the repurposing potential of BRCA drugs that can be repurposed for PD treatment. Chapter 5 is based upon the identification and screening of various FDA-approved anticancer drugs as monoamine oxidase B inhibitors. In chapter 6 of the thesis, we have screened various natural compounds for AD and PD. The library of natural compounds with anticancer properties was prepared from the recent available literature. We filtered the compounds based on their ADMET properties and BBB permeability. Then, molecular docking and molecular dynamics simulations were done to identify the potential compounds. Lastly, chapter 7 summarizes the major findings of this research work from different computational methods with an in-depth discussion of the results. The future perspectives and limitations of our study were also delineated with potential contributions to the science.

CHAPTER II

REVIEW OF LITERATURE

CHAPTER II: REVIEW OF LITERATURE

2.1 INTRODUCTION

Cancer and neurodegeneration are considered as two opposite sides of a flipping coin with some shared tuning. Although the general biology of both the diseases is opposite to each other, many genes and signaling pathways are affected in the same way in both the disorders. Cancer cells are capable of uncontrolled cell proliferation, while neurons face premature cell death. A growing body of literature is available to support the fact that the frequently mutated genes in different NDDs have some link with genes associated with cancer. Epidemiological studies conclude that the diagnosis and treatment of one disease may influence the chances of another condition. Both AD and PD are less common in cancer patients. On the contrary, cancer patients have more risk of certain age-related or other NDDs [6]. The major signaling pathways investigated in cancer pathogenesis have remarkable links with NDDs [7].

Drug repurposing is an emerging approach to redirecting existing drugs to combat difficult-to-treat diseases. There are two main approaches to repurposing. The first approach is the on-target approach to look over the drugs for new therapeutic purposes within the mechanism for which they are approved. The second, more futuristic approach is off-target approach comprising recognition of new therapeutic targets of the existing drugs [8]. The overview of the major strategies is presented in **Figure 2.1**. The repurposing process exploits both computational and experimental methods to explore novel uses of drugs. The succeeding sections highlight the overlapping molecules and signaling mechanisms identified between cancer and neurodegeneration. The mechanisms of various repurposed anticancer drugs in the major NDDs, AD and PD are discussed in detail. The main emphasis

was given on the experimental and clinical studies related to the repurposed drugs. Further, the challenges and disadvantages associated with repurposed drugs are briefly described.

2.2 MOLECULAR CROSSTALK BETWEEN CANCER AND NEURODEGENERATION

The molecular genetics and biological evidence support the fact that a remarkable overlap exists between neurodegeneration and cancer. Out of the two significant connections between cancer and neurodegeneration, one is the shared biological signaling pathways, and the other is the epidemiology of both diseases. The frequently mutated genes associated with different NDDs show a significant connection with cancer-genes, as summarized in **Table 2.1.**

Table 2.1: Interrelationship between the commonly mutated genes in cancer and NDDs.

Protein	Role in cancer	Role in NDDs	References
P^{53}	Tumor suppressor	Downregulation of PS1, upregulation of GSK3β and tau phosphorylation	[9]–[11]
PTEN	Tumor suppressor	Regulation of tau phosphorylation, Neuroprotectant for a dopaminergic system in PD, involved in DNA repair, decreased expression in ALS neurons	[12]–[15]
ATM	Tumor suppressor. Mutated in many cancer types	ATM mutations cause Ataxia Telangiectasia. ATM inactivation causes cerebellar neuronal loss, Reduced activity in AD brains	[16]–[18]
mTOR	Autophagy has a bipolar nature. Both tumor suppressive and oncogenic	Inhibition of autophagy	[19], [20]
Tau	Down expression in certain tumors	The major component of neurofibrillary tangles in AD, co-aggregation with alpha-synuclein in PD	[21]–[23]
APP	Increased non-amyloid genic processing of APP	Increased amyloid genic processing of APP in AD	[24]–[26]
Presenilin	PS1 leads to tumor invasion, and metastasis in cancer, Loss of function of PS2 promotes lung cancer development, regulation of PTEN	Presenilin constitutes the catalytic core of the γ- secretase complex. Aids in APP processing	[27]–[29]
CDK5	Associated with tumor proliferation, angiogenesis, chemotherapy resistance, and antitumor immunity	Causes AD-related pathophysiology hyperphosphorylation of tau and APP	[30]–[34]
Pin 1	Overexpressed, Induction of multiple oncogenic pathways	Downregulated in AD. Aids in tau dephosphorylation. regulates APP processing	[35]–[39]

PARKIN	Downregulated in many cancers, sustain cell proliferation, Stabilize G1/S phase cyclins Promote angiogenesis	The mutation associated with autosomal recessive PD	[40]–[42]
PINK1	Stabilize G2/M and Go/G1 checkpoints and assist in tumor growth	Mutated in familial PD	[43]–[45]
DJ1	A tumor promoter, the attenuator of p53 expression	Loss of function mutation leads to Familial PD, provides neuroprotection in HD	[46]–[48]
HTT	Increases p53 expression	Mutation in CAG repeat within the Htt gene leads to HD	[49], [50]
SOD1	Overexpressed in many cancers, induces mitochondrial unfolded protein response (UPR)	Mutation in Superoxide dismutase1 (SOD1) (an antioxidant enzyme) causes Familial ALS	[51]–[53]
α-synuclein	Expressed in various types of tumors	Misfolded and aggregated in PD. The main component of Lewy bodies and Lewy neurites	[54], [55]
LRRK2	Increased risk of cancer in PD patients with LRRK2 G2019S mutations	Genetic risk factor for familial and sporadic PD	[56], [57]
ATP13A2 (PARK9)	Overexpressed in lung tumor tissue	Downregulation or loss of function mutations result in misfolding and accumulation of α-synuclein	[58], [59]
PLA2G6	Identified as a risk factor for melanoma	Mutations cause PLAN that is classified into four subtypes: ANAD, INAD, adult-onset dystonia-parkinsonism, and AREP.	[60], [61]
TSC1/2	Tumor suppressor	Inhibits mTOR activity	[62], [63]
UCHL1	Tumor suppressor, promotes p53 signaling	Downregulated in AD and PD	[64], [65]
CDK4	Increased expression in various human cancers	Increased expression in AD brains	[66], [67]
CDKN2A ($p14^{ARF}$)	Tumor suppressor	Associated with cognitive decline	[68], [69]
MC1R	Overexpressed in a large number of human melanomas	Neuroprotective in the nigrostriatal dopaminergic system and neuroinflammatory disease models	[70]–[72]
TYR	Loss of activity increases skin cancer susceptibility	Associated with Parkinson's and other neurodegenerative diseases	[73], [74]

Abbreviations: PTEN: Phosphatase and tensin homolog;GSK3β:Glycogen synthase kinase 3 beta; PS: Presenilin; mTOR: The mammalian target of rapamycin;ATM: Ataxia telangiectasia mutated;CDK5:Cyclin-dependent kinase 5;PINK1:PTEN induced kinase 1;DJ1:Protein deglycase;HTT:Huntingtin;SOD1:Superoxide dismutase 1;LRRK2:Leucine rich repeat kinase 2;ATP13A2:ATPase Cation Transporting 13A2; PLA2G6:Phospholipase A2 Group VI;PLAN:PLA2G6-associated neurodegeneration;ANAD:Atypical neuroaxonal dystrophy; INAD: Infantile neuroaxonal dystrophy; AREP :Autosomal recessive early-onset parkinsonism;TSC1/2: Tuberous sclerosis protein;UCHL1:Ubiquitin carboxyl-terminal esterase L1;CDK4: Cyclin dependent kinase; 4;CDKN2A:Cyclin-dependent kinase inhibitor 2A;MC1R:Melanocortin 1 receptor ;TYR: Tyrosinase (oculocutaneous albinism IA)

The most considerably studied cancer-related gene p53 correlates with genes linked with AD, PD, and other NDDs [75], as shown in **Figure 2.1**. Activation of p53 was found to be an astounding molecular feature of NDDs. In the case of Alzheimer's, Amyloid precursor protein (APP) expression is controlled by p53 [76]. The C- terminal intracellular fragment of APP is known to stimulate the promoter activity of p53 gene promoting tau

phosphorylation. Under cellular stress, Mouse double minute 2 homolog (MDM2) levels are low accompanied by increased levels of p53 and Glycogen synthase kinase 3 beta (GSK3β), which phosphorylates tau [11]. An interesting crosstalk exists between p53 and Presenilin (PS) isoforms. P53 expression decreases by PS1, and overexpressed PS2 increases p53 expression [10], [77], [78]. The Parkinson's associated genes parkin, PTEN-induced kinase 1 (PINK1), and Protein deglycase (DJ1) have an essential role in cancer signaling. The expression of PARKIN is downregulated in many cancer types, and it plays a vital role in regulating different hallmarks of cancer- apoptosis, mitochondrial dysfunction, and inflammation [40], [41], [79]. It assists cancer cell proliferation by activating the Akt pathway [80] and by maintaining the stability of G1/S cyclins [81]. PARKIN negatively regulates the activity of the p53 gene in human PD brains and exerts its neuroprotective effects [82]. Like PARKIN, DJ1 expression is also found to be upregulated in many cancers [83]. The gene plays a functional oncogenic role by promoting the Phosphoinositide-3-kinase-protein kinase B/Akt (PI3K-PKB/Akt) signaling pathway [[84]. Another PD-linked gene, PINK1 exerts its tumor-promoting activities dependently or independently of parkin [43], [85]. PINK1 sustains cellular proliferation by regulating cell cycle through G2/M and Go/G1 checkpoints [44].

The molecular association between p53 and other NDDs is less significant than AD and PD. It has been found that ALS associated gene Superoxide dismutase (SOD1) is overexpressed in cancers and plays a vital role in maintaining cellular Reactive oxygen species (ROS) levels [86], [87]. Under mitochondrial stress conditions, SOD1 expression increases to activate mitochondrial Unfolded protein response (UPR) in both ALS and cancer [88]. A study described the role of mutant SOD1 in p53 upregulation [89]. The same episode of p53 alteration was observed in HD. A study pinpoints that the deletion of p53 debilitates mutant Huntingtin (mHtt) expression-associated traits like mitochondrial

dysfunction in p53-/- mice [90], [91]. Reverse transcriptase-polymerase chain reaction (RT-PCR) and microarray results confirmed the higher activity of p53 in ALS disease model animals [92]. Like biological shreds of evidence, epidemiological studies also provide remarkable mechanistic to understand the heterogeneity of complex mechanisms that exist between cancer and neurodegeneration.

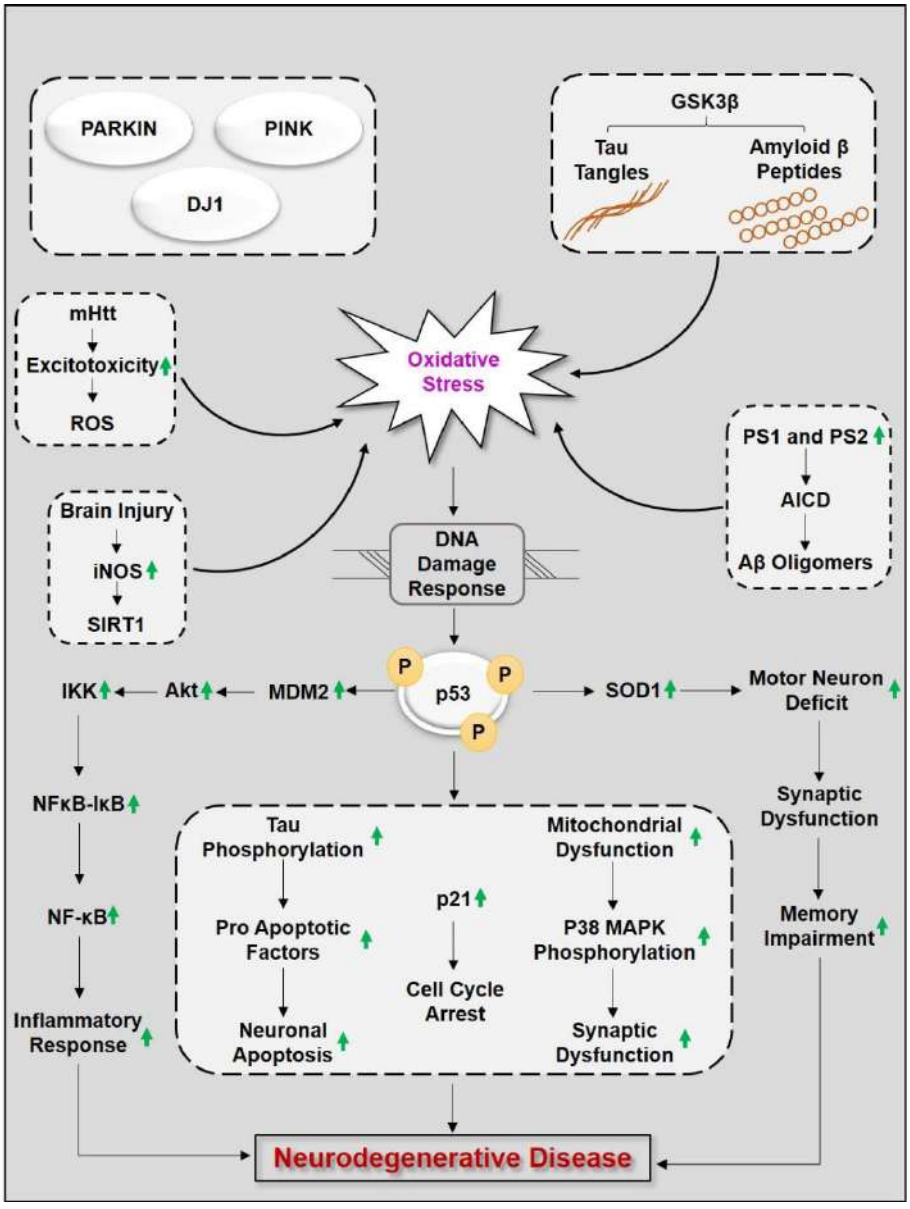


Figure 2.1: The central role of p53 in cancer and neurodegeneration: p53 is an important regulator of cell survival, proliferation, apoptosis, and transcriptional regulation involved in the pathogenesis of life-threatening diseases such as cancer and neurodegenerative disorders. Increased oxidative stress activates DNA damage response, which initiates phosphorylation of p53, which causes neuronal apoptosis, synaptic dysfunction, memory impairment, neuroinflammation, and learning deficits. In AD,

increased expression of Presenilin-1 and Presenilin-2 (PS1 and PS2) causes the generation of β-Amyloid induced toxicity, which results in increased oxidative stress. Amyloid-beta and tau also contribute to oxidative stress. In the case of PD, Parkin, PTEN-induced kinase1 (PINK1), and DJ1 mutations generate oxidative stress conditions. Huntingtin protein also contributes to ROS generation in the case of HD. All the oxidative stress conditions generate DNA damage response and activation of p53. Hyperphosphorylated p53 increases expression of pro-apoptotic factors, NF-κβ, and P38 MAPK, which results in neurodegeneration mediated through neuronal apoptosis, inflammatory response, and synaptic dysfunction, respectively.

A study by Sweden registry focusing on 19000 cases of 18 different types of cancers reported a reduced risk of dementia in cancer patients [93]. Research by Framingham Heart Study Center disclosed a reduced risk of AD in sufferers of 'smoking-related cancers" and a reduced risk of cancers in AD survivors [94]. A study was conducted based on the information available by the Korean National Health Insurance Services (KNHIS) to analyze the association between AD and cancer. The data revealed that the risk of different cancers of the digestive tract, lung, and prostate cancer was significantly reduced for AD patients [95]. A literature-based survey was conducted to study all the epidemiological works for cancer and central nervous system (CNS) disorders. Cancer risk was found to be significantly lower in PD cases except for melanoma, breast cancer, and brain cancers [96]. A concluding work was done on all the available reports on PD and cancer from 1968 to 2009, with 107,598 PD patients. The risk of smoking and nonsmoking-related cancers was reported to be low in PD patients, excluding skin tumors [97]. The epidemiological proofs validating the relatedness of cancer and other NDDs are less. An observational report based on the Utah population database reveals different risk levels linked with various cancers in ALS patients. A decreased risk was observed for lung cancer, an increased risk for salivary and testicular tumors, and an irrelevant risk for melanoma [98]. Except for brain tumors and urinary organ cancers, the chances of cancer occurrence was found to be less in MS patients [99].

2.3 OVERLAPPING SIGNALING PATHWAYS IN CANCER AND NEURODEGENERATION

2.3.1 CELL CYCLE

The cell cycle is a fundamental cellular process typically divided into four phases: Gap 1 (G1) phase, DNA replication (S) phase, gap 2 (G2) phase and lastly cell division (M) phase. The cell cycle is tightly regulated by a series of proteins- the cyclins and the associated cyclin-dependent kinases (cdks) [100]. Cancer is the result of abnormal cell cycle events, characterized by mutations in genes encoding cell cycle proteins or in genes regulating upstream pathways [101]. On the contrary, the premature neurons, once differentiated, remain in a quiescent state for the rest of their life. Under stress conditions, the adult neurons re-enter into the cell cycle, and this results in severe consequences such as cell death and neurodegeneration [102]. Many pieces of evidence have suggested the predominant role of cell cycle malfunctions in various NDDs. The key genes, AβPP, Presenilin 1, and Presenilin 2 (PS1/2) involved in the pathogenesis of AD, are considered as the role players in cell cycle control. In PD, dopaminergic neurons enter the cell cycle but arrest at metaphase, resulting in neuronal apoptosis. Additionally, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated rat neuronal cultures have shown altered expression of proteins required for the G1-M phase transition [103]. Likewise, ALS-associated mutated SOD1 has found to be associated with reduced cell growth, destructive cytoskeletal organization, and aberrant G_2-M transition [104]. It has been suggested that cell cycle aberrations and oxidative stress interact in a complex way that would lead to neurodegeneration and cancer [105].

2.3.2 WNT PATHWAY

The Wingless-type murine-mammary tumor virus integration site (Wnt) is an essential pathway for many cellular functions mostly investigated in cancers such as embryonic

development, tissue development and cellular differentiation [106]. Wnt pathway activation supports tumor proliferation and concurrently protects against neurodegeneration [107]. The Wnt pathway is aberrantly expressed in many cancers and is downregulated in AD, PD, and HD. However, its significance in MS pathogenesis is not clear [108]. The Wnt pathway has a protective role in AD pathogenesis by preventing Aβ induces neurotoxicity. The expression of Wnt ligands and frizzled receptors are found to be downregulated in AD brains [109], [110]. Dysregulated Wnt signaling is also linked with PD pathogenesis [111]. The levels of β-catenin are proposed to be reduced in dopaminergic neurons [112]. A study by Godin et al. suggested that wild type Htt gene induces β-catenin phosphorylation while a mutation in Htt leads to β-catenin accumulation [113]. The altered Wnt pathway has found to be linked with the remyelination process associated with MS.

2.3.3 REDOX SIGNALING PATHWAY

Redox homeostasis plays a crucial role in cellular systems, and any alteration in the signaling processes leads to aging, neurodegeneration, and cancer. Oxidative stress and ROS supports cancer initiation by promoting DNA damage, cancer proliferation by further DNA alteration, and cancer metastasis.AD, PD, HD, and ALS are linked with oxidative damage and impaired redox mechanisms [114]. In AD, increased oxidative stress induces Beta secretase 1 (BACE1) secretion and Aβ production, which further creates oxidative stress [115]. Metals like iron (Fe), copper (Cu), and zinc (Zn) contents are found to be higher in amyloid plaques as compared to the surrounding tissues [116]. In PD, the oxidized products of dopamine generate various free radicals and disturb mitochondrial functions [117]. The levels of different thiols like Glutathione (GSH) are reduced in the case of PD, where these species are important in maintaining redox balance [118], [119]. Accumulation of Fe and dysregulated Ca^{2+} signaling also contribute to the redox imbalance in PD brains

[120], [121]. In the case of ALS, mutant SOD1 is associated with increased oxidative stress. Mutant SOD1 interacts with mitochondria and lessens the reduced/oxidized glutathione (GSH/GSSG) ratio. Increased hydrogen sulfide (H_2S) levels also contribute to oxidative damage in ALS [122].

2.3.4 MAPK PATHWAY

The serine-threonine kinases Mitogen-activated protein kinases (MAPKs) regulate different cellular functions such as cell growth, differentiation, and cell death. The MAPK signaling has three major kinases: MAPK kinase kinase (MAPK3K), MAPK kinase (MAPK2K), and MAPK. The role of different MAPK kinases is widely investigated in tumor biology. Mutations in ERK kinases- B-Raf and K-Ras are frequently observed in many human cancers [123]–[125]. Likewise, MAP kinases have interesting roles in neurodegeneration. In the case of AD, MAP kinases are involved in tau phosphorylation, and tau tangle formation [126]. The mitochondrial dysfunction associated with AD is mainly driven by Extracellular signal regulated kinase (ERK), downregulation of which restores the mitochondrial abnormalities in AD [127], [128]. Under oxidative stress, activated c-Jun N-terminal kinase (JNK) and p38 induce the expression of APP processing BACE1 enzyme. In PD, aggregation of α-syn induces activation of p38, and MAPK which induce expression of different neuroinflammatory cytokines in microglial cells [129]. The activity of JNK kinase is known to be high in dopaminergic neurons, and its function is altered by parkin [130]. JNK and p38 kinases play a dominant role in motor neuron associated abnormalities [131], [132]. p38 promotes ALS progression by inducing nitric oxide (NO) production in motor neurons via Fas-associated apoptosis [133], [134].

2.3.5 ANGIOGENESIS

Angiogenesis is a vital process for tumor cells to maintain their survival and metastasis. Tumor cells overexpress different angiogenic markers such as Vascular endothelial growth

factor (VEGF) and basic fibroblast growth factor (bFGF) [135]. Some recent research identified the role of angiogenic mechanisms in neuroinflammation and neurodegeneration. The angiogenesis inhibitors thalidomide and its similar compounds have shown good experimental results in AD and PD disease models [136]. The literature has numerous studies justifying the neuroprotective role of VEGF. VEGF provides neuroprotection against excitotoxicity via two pathways: PI3K/Akt pathway and MEK/ERK pathway [137]. VEGF and Transforming growth factor-beta (TGFβ) and Tumor necrosis factor-alpha (TNFα) are highly expressed in AD brains [138]. VEGF protects motor neuron death under stress conditions of excitotoxicity, SOD1-induced toxicity, and hypoxia [139], [140]. Studies have suggested that Aβ promotes angiogenesis by Notch signaling and γ secretase pathways [141]. Interesting work was done by David and coworkers, who found increased levels of angiogenic markers in Cerebrospinal fluid (CSF) of PD patients [142].

2.3.6 PI3K/AKT/mTOR PATHWAY

The PI3K/AKT/mTOR pathway is critical for an array for cellular functions such as cell proliferation, grown, survival and metabolism. PI3K family is composed of catalytic subunits (p110α, p110β, p110δ and p110γ) and non-catalytic or regulatory subunits (p85, p87 and p101) [143]. The PI3K signaling is considered as the major controller of cancer. The pathway is interrupted in a wide variety of human cancers through different mechanisms such as inactivation of PTEN, mutation of PI3K, or activation of upstream elements of PI3K [144]. The pathway is also essential for neuronal survival. In Alzheimer's, the PI3K pathway controls cell survival, neurogenesis, oxidative stress, Aβ metabolism, and tau phosphorylation [145]. Aβ exerts neurotoxicity by inhibition of PI3K signaling, and a PI3K activator may provide neuroprotection by activation of the PI3K pathway [146]. A study proposed the role of PI3K/AKT/mTOR pathway in Aβ25-35 induced autophagy.

The mTOR signaling has a potential therapeutic aspect in the brain in the autophagic clearance of polyglutamine protein aggregates in HD [147], clearance of Aβ aggregates in AD [148], and removal of α -syn aggregates in PD [149]. A study by Mammana et al. suggested the therapeutic role of the PI3K/mTOR pathway in immunomodulation and prevention of relapses in MS [150]. The experimental studies in the MS disease model proposed that PI3K signaling has an important role in leukocyte survival [151].

2.3.7 CYTOKINE AND IMMUNE SIGNALING

Cytokines are the small proteins that contribute to different cellular functions like growth, survival, and differentiation at significantly minimal concentrations. Cytokines have both tumor-promoting and tumor-degrading roles and involved in various tumor-associated processes such as angiogenesis, tumor growth, and metastasis, and immunomodulation [152]. Cytokines are the mediators of cellular injury and repair in different neurodegenerative conditions. Cytokines like Interleukin-1 beta (IL-1β) and TNF cause neurotoxicity by inducing glutamate production. Another cytokine TGFβ is associated with the pathogenesis of AD, PD, HD, ALS, and MS [153]. The altered TGFβ signaling in AD contributes to Aβ aggregation, microglial activity, and neurodegeneration [154], [155]. In PD, TGFβ signaling is involved in dopaminergic neuronal survival and development. Studies have identified a higher concentration of TGFβ in symptomatic and asymptomatic HD brains [156], [157]. Reports suggested that astrocytes secrete TGFβ as a neuroprotective mechanism to prevent motor neuron degeneration in ALS [158].

The complement system plays an essential dual role in cancer, having antitumor and pro-tumor activities. The complement system mediates inflammation associated with tumor progression and regulates the response of T cells for tumors [159]. Complement dysregulation has a vital link with neurodegeneration as well. The aberrant activation of the complement cascade in the AD mouse model is associated with cognitive deficits and

synaptic dysfunction [160]. Aβ is a potent stimulator of the complement pathway, and inhibiting complement signaling helps to reduce AD-associated symptoms such as cognitive deficits and microglial activation [161].

2.4 NEUROPROTECTIVE MECHANISMS OF REPURPOSED ANTICANCER DRUGS IN DIFFERENT NEURODEGENERATIVE DISORDERS

Several studies have been conducted to identify the prospective role of different anticancer drugs for AD, PD, ALS, MS, and HD treatment as summarized in (**Table 2.2 and Figure 2.2).** The following sections highlight different research works conducted in this context.

Table 2.2: Neuroprotective role of different anticancer drugs in various neurodegenerative disorders

Drug	Drug class	Role in Cancer	Pathways Involved	Role in NDDs	Type of NDDs	References
5-Fluorouracil	Antimetabolite	Inhibits DNA and RNA synthesis	DNA synthesis pathway	Improves motor activities	ALS	[162] [163]
Alemtuzumab	Monoclonal antibody	Causes CD52 cell lysis and lymphocyte depletion	Inflammatory response pathway	Immunosuppression and immunomodulation	MS	[164] [165]
Bexarotene	Retinoid X receptor agonist	Inhibits cell cycle progression, prevents multidrug resistance, inhibits angiogenesis and metastasis	p53/p73 pathway	Reduces Aβ and huntingtin levels, Promote microglial phagocytosis and improves motor functions	AD, HD	[166], [167]
Carmustine	Alkylating agent, DNA crosslinking agent	Tumor growth inhibitor. Inhibit DNA replication and transcription.	DNA synthesis pathway	Reduces Aβ production	AD	[168]
Cladribine	Nucleoside analog	Inhibits lymphocyte proliferation by inhibiting DNA synthesis and DNA repair	DNA synthesis pathway	Reduces circulating B and T lymphocytes, Neuroprotectant	MS	[169]
Cyclo-Phosphamide	Alkylating agent, Inhibits cell division	Inhibits nucleic acid synthesis. Induces DNA damage and base mispairing	Inflammatory response and cell cycle pathway	Immunosuppression and immunomodulation	MS	[170] [171]
Dactolisib	PI3K and mTOR inhibitor	Inhibits autophagy, interferes with DNA repair and stops the proliferation of cancer cells	PI3K/Akt/mTOR pathway	Reduced memory impairment, decreases microglial activation and lowers IL-10 levels	AD	[172]–[174]
Dasatinib	Tyrosine kinase inhibitor	Inhibits the kinase signaling of Bcr-Abl and Src kinases	JAK-STAT, MAPK and PI3K-Akt pathway	Inhibits amyloid dependent microgliosis	AD	[175] [176]
Dabrafenib	Tyrosine kinase inhibitor	Inhibits MAPK signaling and causes cell cycle arrest	MAPK/ERK pathway	Neuroprotectant, Activates Extracellular signal regulated kinase (ERK), Inhibits c-Jun N	PD	[177]

				terminal kinase (JNK/c-Jun) phosphorylation		
Epothilone D	Microtubule-stabilizing agent	Stops cell cycle by binding to tubulin in cancer cells leading to apoptosis	Cell cycle	Reduced axonal dystrophy and increases axonal microtubule density improving axonal transport and cognitive function	AD	[178], [179]
Erlotinib	EGFR inhibitor	Inhibits the tyrosine kinase activity of EGFR	JAK-STAT, MAPK and PI3K-Akt pathway	Improves survival in SOD1 mouse	ALS	[180] [181]
Imatinib	Tyrosine kinase inhibitor	Inhibits leukemogenesis by targeting downstream signaling of Abl kinase	JAK-STAT, Ras/MAPK, PI3K-Akt, and Src-Pax-Fak-Rac pathway	Inhibition of γ-secretase activity, reduction of soluble SOD1	AD, ALD	[182], [183]
Lonafarnib	Farnesyl transferase inhibitor	Blocks post-translational modification of Ras and inactivates it	Rhes pathway	Activates lysosomes and decreases tau pathology	AD	[184] [185]
Mitoxantrone	Topoisomerase II inhibitor	Inhibits DNA synthesis and DNA repair	Inflammatory response and DNA synthesis pathway	Immunosuppression and immunomodulation, Improves neurological disability	MS	[186] [187]
Methotrexate	Dihydrofolate reductase inhibitor	Inhibits Nucleic acid and protein synthesis	Folate pathway	Immunosuppressant, reduction in serum creatine kinase concentrations	MS	[188] [189]
Nilotinib	Tyrosine kinase receptor	Anti-proliferative action by inhibiting different tyrosine kinases	JAK-STAT, MAPK and PI3K-Akt pathway	Reduction of Aβ and α-syn. Decreases parkin solubility, and restore dopamine levels	AD, PD	[190] [191]
Paclitaxel	Microtubule inhibitor, Bcl-2 inhibitor	Inhibits cell cycle progression by inducing mitotic arrest	Neuroprotective, reduction in tau hyper-phosphorylation	PI3K/AKT, MAPK and EGFR pathway	AD	[192] [193]
Pazopanib	Tyrosine kinase inhibitor	Inhibits Raf-MAPK/ERK pathway	JAK-STAT, MAPK and PI3K-Akt pathway	Acetylcholinesterase inhibitor, Reduces tau hyper-phosphorylation	AD	[194] [195]
Rituximab	Monoclonal antibody	Induces CD20 cell death, cytotoxicity, and apoptosis	Reduction in B cell population	Complement dependent cytotoxicity	MS	[196] [197]
Sunitinib	Tyrosine kinase inhibitor	Stops tumor cell proliferation and angiogenesis	JAK-STAT, MAPK and PI3K-Akt pathway	Acetylcholinesterase inhibitor, an Angiogenesis inhibitor, Inhibits Nitric oxide production	AD	[198] [199]
Saracatinib	Src and Bcr-Abl tyrosine-kinase inhibitor	Anti- invasive and anti-tumor	JAK-STAT, MAPK and PI3K-Akt pathway	Rescues spatial memory deficits and synapse loss	AD, PD	[200], [201]
Tamibarotene	Retinoid x Receptor agonist	Inhibits retinoid signaling	Retinoid signaling pathways	Reduction in Aβ, Reduction in neuroinflammation	AD	[202]
Thalidomide	TNF alpha inhibitor, an Angiogenesis inhibitor	Inhibits angiogenesis and cytokine production. Immunomodulation.	Ubiquitin/ Proteasome System	Reduction of Aβ, Microglial activation, Beta secretase 1(BACE1) enzyme inhibition.	AD	[203] [204] [205]

2.4.1 ALZHEIMER'S DISEASE

Studies have been conducted to identify the prospective role of different anticancer drugs for AD treatment in both *in-vitro* and *in-vivo* conditions. The two retinoid X Receptor (RXR) agonists bexarotene and tamibarotene exhibited neuroprotective properties. Bexarotene induces changes in expression of genes that cause cellular differentiation, reduced cell proliferation, apoptosis, and tumor growth inhibition. It has been described that orally administered bexarotene in an AD mouse model resulted in the clearance of amyloid-beta (Aβ) in an Apolipoprotein E (ApoE)-dependent manner. The ApoE glycoprotein has high expression in the liver and brain. Microglia and astrocytes express ApoE protein. ApoE functions as an Aβ binding protein and accelerates Aβ deposition in amyloid plaques. Bexarotene facilitates Aβ clearance by transcriptionally activating peroxisome proliferator-activated receptor gamma-Retinoid X receptor (PPARγ-RXR) and liver X receptor-Retinoid X receptor (LXR:RXR) and increased expression of ApoE, ATP-binding cassette transporter 1 (ABCA1) and ATP binding cassette sub-family G member 1 (ABCG1) genes [206]. In a study, bexarotene at a concentration of 300mg was given to two different groups: ApoE carriers and ApoE non-carriers. The drug reduced plaque burden in apoE4 non-carriers. The authors noted that the plaques in ApoE4 carriers are harder to solubilize due to compactness [207].

Tamibarotene (Am80) a retinoic acid receptor (RAR) α/β agonist approved in Japan for the treatment of Acute Promyelocytic Leukemia (APL). Am80, a multi-target drug, maybe a potent therapeutic for AD treatment. A study on APP23 mice describes that Am80 reduces extracellular insoluble Aβ (42), but no effects were observed on the soluble Aβ levels. The decrease in extracellular Aβ may be due to increased α-secretase transcription or phagocytosis by activated microglial cells [208]. A study on nilotinib in mice suggested that the drug facilitates autophagy and triggers increased parkin levels thus helping to

reduce Aβ and tau protein levels in AD brains. Nilotinib inhibits c-Abl tyrosine kinase and helps to stabilize parkin-beclin1 interaction that leads to autophagic clearance of Aβ and tau proteins. Work in human embryonic stem-cell-derived AD models showed that nilotinib could recover the synaptic dysfunction and increases the expression of Ras-related protein Rab-3A (RAB3A). An ongoing clinical trial was conducted at Georgetown University in 2017 to evaluate the role of nilotinib in the clearance of Aβ plaques and tau tangles in AD brain patients. [209], [210].

Another work on 3, 6' dithalidomide describes that the drug reduced many hallmark characters of AD-like tau phosphorylation, Aβ accumulation, Aβ plaque number, and memory deficits in AD mice. Treatment with both thalidomide and 3, 6-DT produced a decrease in some activated microglia cells. The activated microglial cells release toxic ROS and proteolytic enzymes to enhance the processing of APP into Aβ peptide [211]. A National Institutes of Health (NIH) supported a 24-week, double-blind, randomized, placebo-controlled phase 2 clinical trial was conducted on 185 subjects with mild to moderate AD. The outcome was that thalidomide with a maximum dose of 400mg/day reduces amyloidogenesis, but it has not been well tolerated by the patients. The results suggested that there was no significant cognitive impairment in the thalidomide treated group [212]. Another drug, imatinib (Gleevec) reduces Aβ levels by indirect inhibition of the γ-secretase enzyme and by producing APP variants. The *in vitro* results with imatinib were not reproducible due to its poor brain penetration [213], [214].

Acetylcholinesterase (AChE) inhibitors are the widely explored drugs developed for AD. Sunitinib is an anticancer drug approved by the FDA for the treatment of metastatic renal cell carcinoma and Imatinib-resistant gastrointestinal tumors and had shown success as an anti-Ache drug. Studies have suggested that Sunitinib may be a potential drug for treating NDDs [215]. Work on two AD animal models, tg2576 and 3xTgAD mice showed that

Sunitinib improves cognitive performance [216]. A study demonstrated that in the scopolamine-induced mouse model, Sunitinib decreased the activity of AChE. Molecular docking analysis revealed that Sunitinib interacts with the catalytic anion site (CAS) and peripheral anion site (PAS) of Ache [198]. It was investigated in HIV models of neurotoxicity that sunitinib inhibited CDK5 activity and tau hyper-phosphorylation [217]. Sunitinib is also an antiangiogenic agent and can be used as a therapeutic for AD as neo-angiogenesis and hyper vascularization are associated pathological conditions with AD. Sunitinib alters the levels of Aβ secreted from endothelial cells by inhibiting VEGF signaling [141]. Pazopanib, another tyrosine kinase inhibitor, inhibits AChE and restores cognitive deficits to the same extent as donepezil. A study has shown that pazopanib reduces phosphorylated tau levels and modulates astrocytic activity in the AD mouse model [194], [218]. Another chemotherapeutic FDA-approved drug carmustine (BCNU), is used to treat some types of brain tumors, lymphomas, myelomas, and metastatic brain tumors. BCNU is an alkylating agent responsible for DNA disruption, cell cycle arrest, and apoptosis. A study demonstrated that BCNU decreases Aβ levels by altering APP trafficking and cleavage. *In vitro* and *in vivo* activity of BCNU is independent of the secretase (α, β, and ϒ) enzymes. The main advantage is that there are no side effects of carmustine as seen with secretase inhibitors and it is a blood-brain barrier (BBB) penetrant drug. Thus, BCNU may be a favorable anti-Aβ drug [168].

Paclitaxel (Taxol), a further antineoplastic agent, is a microtubule inhibitor commercially available for the treatment of breast, pancreas, ovarian, lung, and cervical cancer. Paclitaxel alters the dynamic stability of microtubules by binding to the β subunit of tubulin [219]. Research showed that it causes inhibition of cell division and apoptosis in cancer cells. An experimental study by Angiotech Pharmaceuticals describes that paclitaxel positively affects movement disorders such as Alzheimer's. A group led by Michaelis conducted

experiments to show that Taxol helps to slow down the degeneration of nerve cell branching ends. A study proposed that Taxol reduces Aβ toxicity by inhibition of Aβ-induced activation of calpain, which reduces the proteolysis of p35 to p25 and decreased activation of CDK5/p25 complex. The reduced activity of CDK5/p25 complex helps to minimize tau phosphorylation and disease progression [192]. The potential of Taxol as an AD therapeutic is limited due to its poor bioavailability to the brain and penetrant Taxol analogs are suggested to be used in AD treatment.

2.4.2 PARKINSON'S DISEASE

One of the most accepted hypotheses for the progression of PD is the accumulation of alpha-synuclein, which increases oxidative stress and eventually leads to dopaminergic neuronal cell death. In an animal model, it was demonstrated that knockdown of c-Abl, which phosphorylates parkin, leads to mitochondrial apoptotic signaling cascade resulting in mitochondrial dysfunction and cell death via three potent mechanisms. It leads to suppression of parkin phosphorylation, upregulation of parkin interacting substrates, and inhibiting the activity of aminoacyl-tRNA synthetase complex-interacting multifunctional protein 2 (AIMP-2) [220]–[222]. Nilotinib, an anticancer drug targeting c-Abl, prevents alpha-synuclein aggregation and neuronal cell death, which improve memory and cognitive defects in the PD disease model [223].

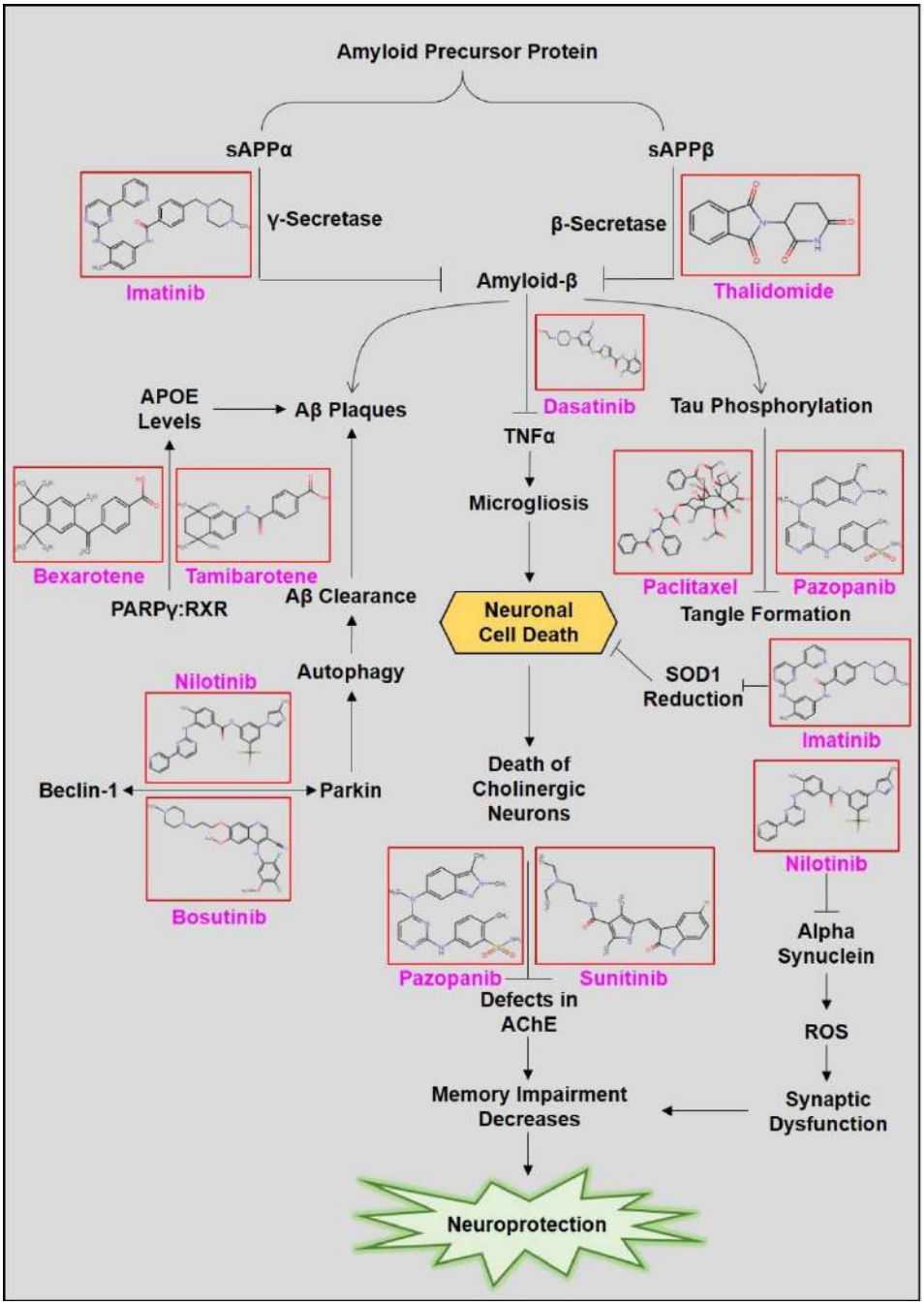


Figure 2.2: Schematic representation of the repurposed anticancer drugs in neurodegenerative disorders: Pointed arrows represent pathway activation and blunt arrows represent pathway inhibition. Aβ clearance, inhibition of tau hyper-phosphorylation, and APP processing are the significant events targeted by anticancer drugs in AD. α–syn aggregation and SOD1 mutation are inhibited in the case of PD and ALS, respectively. Thalidomide and Imatinib reduce Aβ levels in AD. Bexarotene and Tamibarotene help to increase APOE levels. Nilotinib and Bosutinib enhance the interaction of beclin-1 and parkin and help in amelioration of Aβ peptides. Both Sunitinib and Pazopanib inhibit the activity of Acetylcholinesterase (Ache). Paclitaxel and Pazopanib both reduce tangle synthesis by inhibiting tau hyper-phosphorylation. Dasatinib exerts neuroprotection in AD by inhibiting microgliosis. In PD, Nilotinib reduces α-syn aggregation. In ALS, Imatinib reduces SOD1 mutational changes.

In another study, it was found that under oxidative stress conditions, c-Abl phosphorylates parkin, regulates its cytoprotective function, and inhibits ubiquitin-dependent degradation. A clinical study was conducted to test the potential of nilotinib in 12 PD patients. The results showed good brain permeation and pathological significance with some side effects [224]. An *in silico* study concluded the neuroprotective properties of dabrafenib for PD. Dabrafenib shows its neuroprotective function by inhibition of the phosphorylation of JNK/c-Jun and by activating ERK *in vitro* and *in vivo* [177].

2.4.3 AMYOTROPHIC LATERAL SCLEROSIS

ALS is a neurodegenerative disorder characterized by loss of motor neurons, also called Lou Gehrig's or Charcot disease, which decreases muscle movement and size. Being an untreated disorder, drug discovery through drug repositioning has been of utmost importance, especially for anticancer drugs because of similarity up to some extent in disease progression. A research was conducted to validate the potency of imatinib and related inhibitors (dasatinib and bosutinib) in ALS mouse models. Imatinib showed good results with a significant reduction of soluble SOD1. A study on the mouse antimetabolite anticancer drug 5-fluorouracil (5-FU) in mice models of ALS suggests that the drug improves motor performance; still, the mechanism of action was not precise [162]. Scientists from Ben Gurion University marks a statement that rituximab, an anticancer drug restores the primary immune cells of the brain and helps to extend the life expectancy of ALS patients. Another chemotherapeutic agent masitinib is a potent regulator of mast cell and microglial cell activity. The clinical results have shown the neuroprotective role of masitinib in ALS. A compelling report was published in the 2019 Muscular Dystrophy Association Conference that masitinib is capable of regulating the action of macrophages, neutrophils, mast cells, and Schwann cells- all the four responsible for neurogenic inflammation [225], [226]. A phase II clinical trial was initiated to determine the anti-

neuroinflammatory properties of thalidomide in ALS patients. The drug may have a possible role as a neuroinflammation inhibition agent [227].

2.4.4 MULTIPLE SCLEROSIS

MS is an autoimmune neurodegenerative disorder that remains untreated. Drug repurposing using anticancer was found to be a promising therapeutic strategy against multiple sclerosis. To date, six anticancer drugs, namely mitoxantrone, alemtuzumab, cyclophosphamide, cladribine, rituximab, and methotrexate, are investigated for MS. Alemtuzumab, a monoclonal antibody targeted against CD-52 has excellent promise for MS [165], [228]–[230]. A recent review reported the efficacy of Alemtuzumab as a disease-modifying drug for MS highlighting its biological and clinical importance [231]. The phase II/III clinical trials supported the safety profile of the drug for MS treatment with mild to moderate infection problems [232]. Another monoclonal antibody (mAb) rituximab helps to reduce the relapse rate and disease advancement in MS [233]. A further study confirms that rituximab depletes B cell populations in MS patients [197]. Mitoxantrone, a chemotherapeutic agent, got approval for its use in MS. A clinical trial using mitoxantrone on MS patients concluded that it was able to reduce the risk of disease progression up to some extent without any sign of melanoma or other types of tumors with minimum side effects of drug dosage. The study gained evidence after ten years of treatment, which concluded that mitoxantrone is a safe and effective treatment against the patient with relapsing-remitting MS (RRMS) [234], [235]. Cyclophosphamide (CYC), an anti-replicative anti-mitotic agent also showed anti-inflammatory action by increasing the production of inflammatory cytokines and increasing the secretion of anti-inflammatory cytokines [236]. CYC can cross the BBB and has good bioavailability in the brain and help to stop MS progression [170], [171], [237]. Cladribine and methotrexate also advocate their potential benefit in different studies, but the exact mechanism of their action in MS is not

precise yet [169], [188], [238]–[240]. A study suggested the role of imatinib in MS treatment also. Treatment of Experimental Autoimmune Encephalomyelitis (EAE), an MS animal model, with imatinib showed notable inhibition in disease progression [241].

2.4.5 HUNTINGTON'S DISEASE

A little information is available regarding the significance of anticancer drugs in HD pathophysiology. A phase 1 clinical trial is recruiting at the Georgetown University Medical Center (GUMC) to check the safety and efficacy of nilotinib in HD patients. The work is based on the fact that nilotinib reduces the protein aggregation in PD and dementia with Lewy bodies and may reduce huntingtin protein accumulation.

Till now, a number of anticancer drugs have entered in clinical studies for different NDDs. The complete list of drugs is provided in **Table 2.3**

Table 2.3: List of clinical trials conducted with anticancer drugs for the major five NDDs (Adapted from ClinicalTrials.gov)

S. No.	Study	Clinical Phase	Study Design	Status	Results
1	NCT02947893 (Nilotinib)	Phase II	Total of 42 participants with mild to moderate AD. Twenty-one patients assigned to group 1 treated with the placebo drug one capsule every day for 6 months. Two capsules every day for the subsequent 6 months.	Active but not recruiting	Expected result-Nilotinib will be a therapeutic candidate for AD via c-Abl inhibition.
2	NCTO1782742 (Bexarotene)	Phase II	Total of 20 participants. Given 75 mg of Bexarotene for one week followed by 150mg for weeks 2 to 4. Open-label phase for weeks 5 to 8 (150 mg drug for four weeks) one placebo capsule for week 1. two tablets for weeks 2 to 4. An open-label phase of weeks 5 to 8 (150mg drug for four weeks)	completed	Significant reduction in brain amyloid burden in ApoE4 carriers. An increase in serum triglycerides in Bexarotene treated patients.
3	NCT01094340 (Thalidomide)	Phase II/III	Total of 20 participants. Given a fixed dose of thalidomide for 24 weeks.	Unknown	Expected results-effective AD drug
4	NCT01120002 (Tamibarotene)	Phase II	Total of 50 participants. Given Tamibarotene (2mg) & placebo capsule every day.	unknown	Expected results-effective AD drug

5	NCT02281474 (Nilotinib)	Phase I	Oral nilotinib was given to patients daily for six months	completed	Results not available. Expected results- an effective and safe drug for PD
6	NCT03205488 (Nilotinib)	Phase II	A total of 75 participants were assigned to 3 different groups. Received daily dose of placebo, nilotinib (150mg), and nilotinib (300mg) for 12 months period.	Active but not recruiting	Expected results- an effective and safe drug for PD Improvement in motor symptoms
7	NCT02588677 (Masitinib)	Phase II/III	Experimental drug masitinib was given to 394 participants along with riluzole at two different doses-masitinib 3mg/kg/day and masitinib-4.5mg/kg/day	Completed	Results not available. Expected results- an effective and safe drug for ALS
8	NCT00140452 (Thalidomide)	Phase II	Thalidomide tablets were given to 40 ALS patients for a 12-week period with an initial dose of 100 mg for six weeks and a progressive increase of 50 mg per week until 400mg/day dose.	Terminated	Results not available.
9	NCT03674099 (Imatinib)	Phase II	Imatinib (400mg) will be given twice daily for 14 days along with methylprednisolone	Recruiting	Results not available. Expected results- Imatinib would be more efficient than methylprednisolone for MS treatment
10	NCT03979456 (Rituximab)	Phase III	200 participants receiving rituximab(500mg) for four years	Recruiting	Expected results- an effective and safe drug for MS
11	NCT03193086 (Alemtuzumab)	Phase I	Total of 35 participants. Initial treatment with 60 mg alemtuzumab over a five-day course followed by 36 mg intervention of the drug over a three-day course.	Recruiting	Expected results- an effective and safe drug for MS with good blood-brain barrier permeability
12	NCT00436826 (Cladribine)	Phase II	Two hundred participants already receiving IFN-beta therapy were given 3.5mg/kg total dose of cladribine along with placebo and IFN-β (44mcg) thrice a week.	Completed	Decreased relapses, reduced MRI lesion activity with some side effects like lymphopenia
13	NCT01433497 (Masitinib)	Phase III	Total of 656 patients in 2 experimental groups. Group 1 received masitinib (4.5mg/kg) twice daily, while patients in group 2 received increased dose (6mg/kg) after three months. Placebo was given the same dose.	Active but not recruiting	Expected results- safe and effective drug for primary progressive multiple sclerosis (PPMS) & secondary progressive multiple sclerosis (SPMS)
14	NCT04063124 (Dasatinib+Quercetin)	Phase I/II	Total 40 participants were given combination treatment of D& Q for 2 days on/14 days off for 12 weeks.	Recruiting	Expected results- reduction in CSF biomarkers of AD

15	NCT03888222 (Bosutinib)	Phase II	A total of 30 participants was divided into three groups (n=10). Each group was treated with Bosutinib/placebo with two doses of 100mg and 200 mg. Further randomization into groups each with n=15	Recruiting	Expected results-effective drug for the treatment of Lewy body Dementia
16	NCT01864655 (Saracatinib)	Phase I	24 participants divided into three following groups; each was given Saracatinib at doses of 50 mg, 100 mg, 125 mg or placebo daily for 4 weeks.	Completed	Saracatinib was reasonably safe and well-tolerated in mild to moderate AD patients
17	NCT03661125 (Saracatinib)	Phase I	30 participants are divided into two groups. In first arm of study one group would be given 100 mg Saracatinib for 2 weeks while other would be given placebo. In second arm, groups would cross over, that is, the group that were given drug in first arm would be given placebo and other would be given 100 mg drug for 2 week.	Recruiting	Expected results-effective drug for the treatment of PD

2.5 KINASE INHIBITOR THERAPEUTICS FOR CANCER AND NEURODEGENERATIVE DISORDERS

Protein kinases are a distinct class of enzymes that play an integral role in different cellular processes, and their dysregulation is associated with various pathological conditions. The role of kinase inhibitors in cancer is well established, where they regulate the activity of kinases involved in uncontrolled cell division, proliferation, and invasion [242] [243]. Thus far, most of the kinase inhibitors are approved for oncology indications; however, some of them have recently gained attention in Rheumatoid arthritis, inflammatory disorders, and several chronic neurodegenerative disorders. It has been suggested that protein kinases play an essential role in the significant domains related to AD, such as tau phosphorylation, APP processing, neuroinflammation, and neurotoxicity. For instance, GSK3 and CDK5 have been studied concerning tau phosphorylation and APP processing [244]. GSK3 inhibitors have been reported to be useful in ALS as well, where they delayed the onset of disease. Similarly, the role of CDK5 has also been confirmed in PD and HD, where it is the mediator of dopamine and glutamate neurotoxicity [245] [246].

p38 Mitogen-activated protein kinase (p38 MAPK) is another kinase of interest in neuroinflammation where it regulates the synthesis of inflammatory cytokines such as TNF-α. Activation of p38 MAPK has also been reported in astrocytes and neurons during cerebral ischemia [247]. Significant studies have demonstrated the role of Abelson non-receptor tyrosine kinases (Abl) kinases in neurodegenerative disorders [248], [249]**.** Several studies have shown that mutation in c-Abl leads to defective neurogenesis and different deleterious neurological phenotypes [250]. Abl was found to be upregulated in the brain region and causes loss of neuronal cells, impaired motor activity, cognitive dysfunction, and learning deficits which could be reversed by the potential action of c-Abl inhibitors. c-Abl inhibitors inhibit the phosphorylation of CDK5, regulate the phosphorylation of alpha-synuclein, Parkin, and associated substrates such as the NLR family pyrin domain containing 3 (NLRP3), Parkin interacting substrate (PARIS), AIMP2, Poly (ADP ribose) (PARP) and JNK/p38. [190], [251]–[253]. Similarly, ERK is thought to be involved in the regulation of neuronal apoptosis. Studies have shown the presence of activated ERKs in the initial stages of neurofibrillary tangle formation in AD brains. JNK3, a member of the MAPK pathway, is highly expressed in the brain. A study with jnk3 mutant mice has shown protection against 6-hydroxydopamine and MPTP in the dopaminergic neurons in the substantia nigra [254].

Repurposing of kinase inhibitors for the treatment of NDDs is an area of interest for the research community. Several kinase inhibitors have shown success in experimental and clinical studies and have demonstrated their protective effect against signaling mechanisms associated with NDDs. Angiogenesis, PI3/Akt pathway, MAPK pathway, inflammatory response are the major pathways targeted by kinase inhibitors in both Cancer and neurodegenerative disorders, suggesting their potential repurposing roles. The proposed

mechanisms of various kinase inhibitors in neuroprotective pathways are highlighted in **Figure 2.3**.

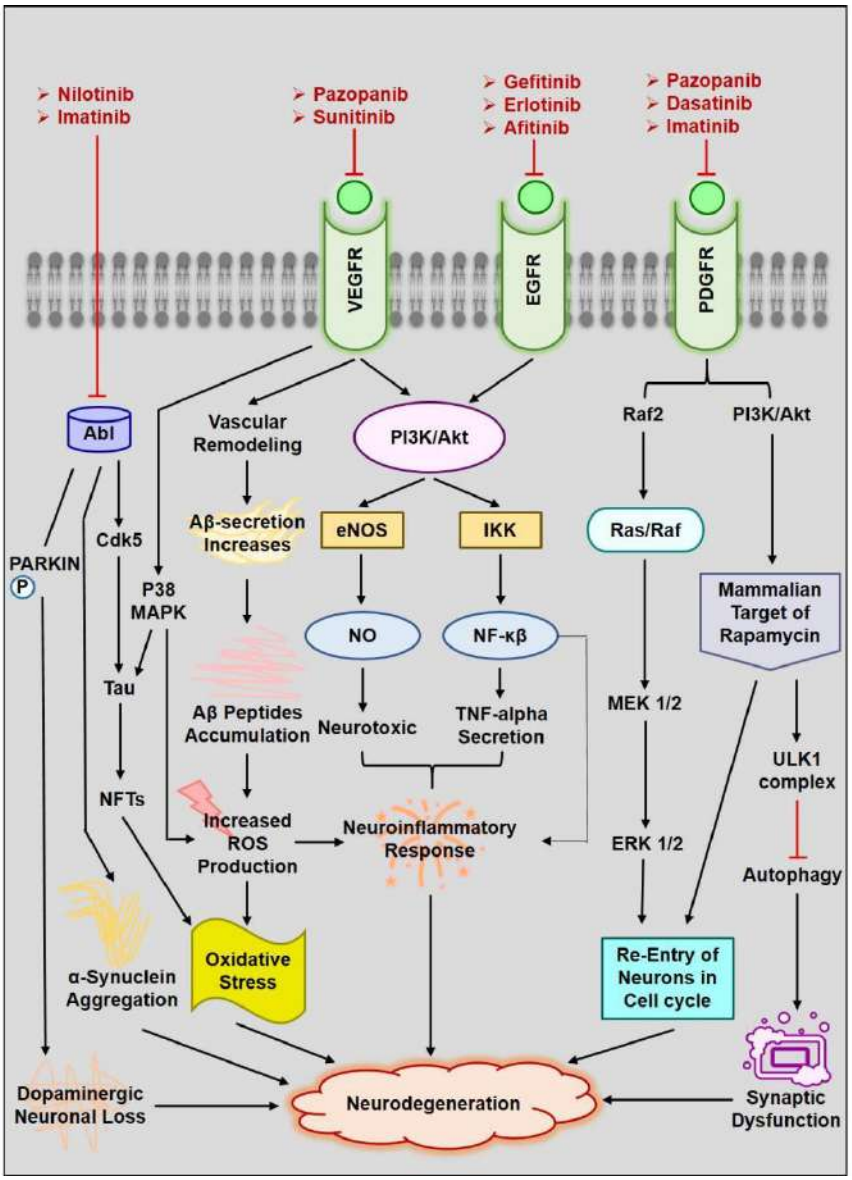


Figure 2.3: Proposed mechanism of kinase inhibitors in neuroprotection: Pharmacological inhibition of c-Abl with anticancer drug Nilotinib and Imatinib helps to prevent neurofibrillary tangle formation by inhibition of CDK-5 activity. The drugs inhibit PARKIN phosphorylation and compensate for the dopaminergic neuronal loss. Inhibition of Vascular endothelial growth factor receptor (VEGFR) by Pazopanib and Sunitinib may ameliorate Nitric Oxide (NO) toxicity, prevent the release of inflammatory cytokines by the inhibition of p38 kinase, and reduction in ROS production. Gefitinib, Erlotinib, and Afatinib are the Epidermal growth factor receptors (EGFR) that can reduce neuroinflammatory response by inhibition of Tumor necrosis factor-alpha (TNF-α) and also reduce amyloidogenesis. The inhibition of Platelet-derived growth factor receptor (PDGFR) by Pazopanib, Dasatinib, and Imatinib have neuroprotective roles in phosphoinositide-3-kinase/Aky (PI3/A-kt) pathway inhibition that leads to mTOR mediated activation of autophagy and also stop post-mitotic neurons from re-entering in the cell cycle. All the events trigger neuroinflammation and neuronal cell death associated with neurodegeneration.

2.6 PROTECTIVE ROLE OF ANTICANCER DRUGS AGAINST NEUROTOXINS

Neurotoxins such as glutamate, domoic acid, amyloid-beta, alpha-synuclein, β-N-Methylamino-L-alanine, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine,1-methyl-4-phenylpyridinium, rotenone,3-Nitropropionic acid, NO and free radicals induce neuronal injury and neuronal toxicity through different mechanisms such as mitochondrial dysfunction, apoptosis, autophagy clearance, and oxidative stress. However, a few anticancer drugs are identified to date, which overcomes the adverse effects of these neurotoxins and provides neuroprotection, as depicted in **Figure 2.4**. NO is a neurotransmitter vital for normal brain functioning. Still, excessive production of NO is associated with the pathogenesis of AD, PD, and MS [255]. In Alzheimer's brain, Aβ stimulates NO production, which leads to mitochondrial dysfunction and causes neurotoxicity [256]. Prolonged exposure of SHSY5Y cells to NO generates tau neuro-pathogenesis by induction of tau oligomers formation [257]. NO is responsible for neuronal death of dopaminergic and motor neuron loss associated with PD and ALS, respectively [258]. A study shows an increase in Reactive nitrogen species (RNS) in the CSF of MS patients' brains [259]. A work by Chinese researchers confirmed that Sunitinib blocks NO overproduction by inhibiting neuronal Nitric oxide synthase (nNOS) [199] The neurotoxic effects of oxidative stress in neurological conditions are confirmed by many studies. Oxidative stress created by reactive oxygen species (ROS) release free radicals that contribute to disease pathogenesis by effecting different cellular functions. The major adverse effects are mitochondrial dysfunction and inhibition of the electron transport chain [260]–[262]. Aβ and alpha-synuclein are the significant neurotoxins associated with AD and PD pathology. The intracellular Aβ oligomers exert their toxic effects by proteasome dysfunction, tau hyper-phosphorylation, lipid peroxidation, altered tau aggregation, and endothelial cell damage [263], [264].

Similarly, α-syn, in PD brains, is responsible for autophagy inhibition, mitochondrial dysfunction, inhibition of the proteasome, oxidative stress, and neuroinflammation [265]. Anticancer drugs Bexarotene, Thalidomide, Tamibarotene, and Nilotinib can reduce toxic levels of Aβ, while Nilotinib also clears α- syn from the brain. Another factor contributing to neuronal toxicity is the microglial cell. Microglia are the professional phagocytic cells of the CNS but depending on the environmental conditions exert neurotoxic effects. Microglia release several ROS as NO, peroxynitrite, hydrogen peroxide, and superoxide that leads to oxidative damage. These cells also cause excito-neurotoxicity by secreting glutamate [266]. Dactolisib, an anticancer tyrosine kinase inhibitor reduces microglial activation and Aβ plaques in AD mice [267].

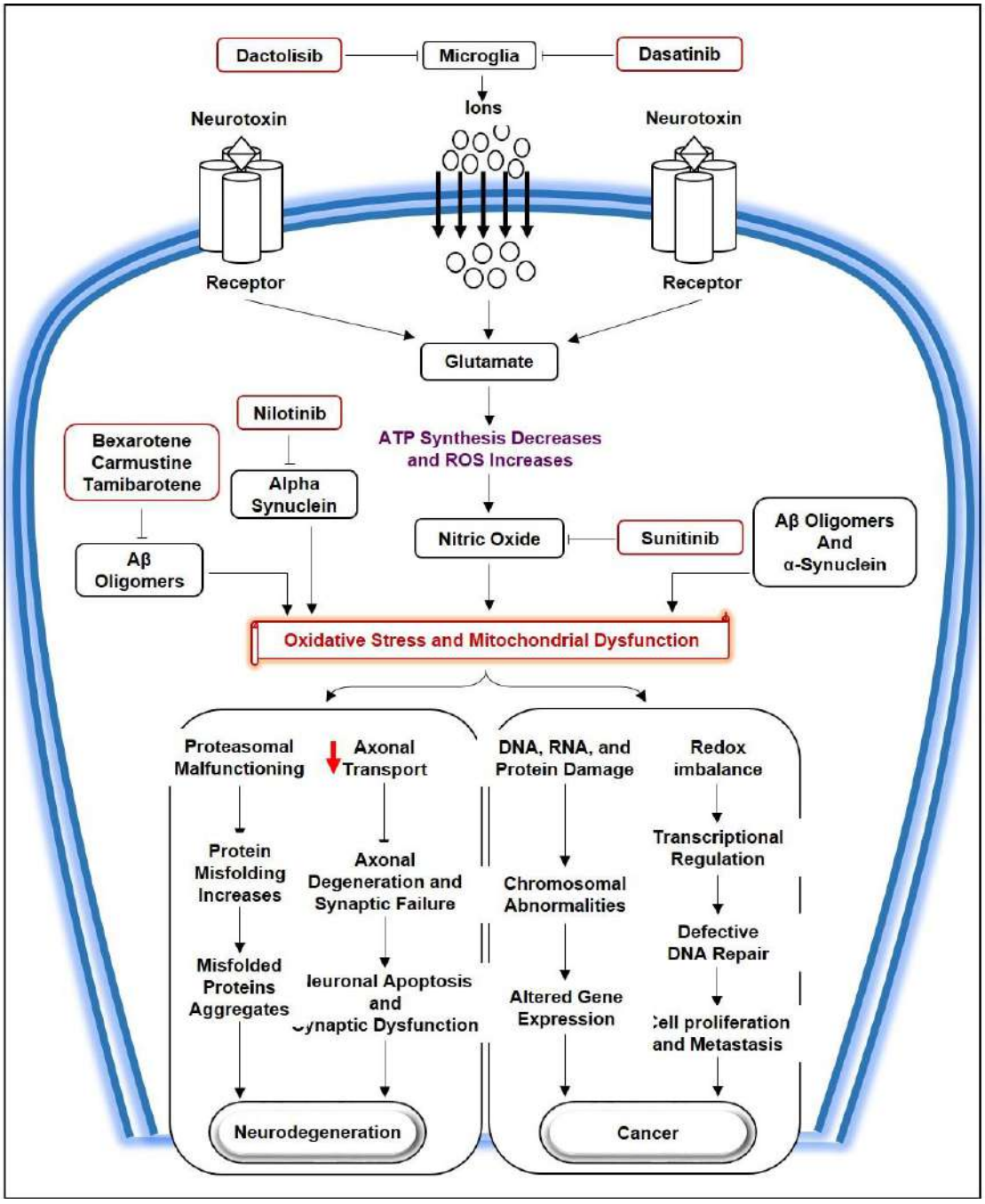


Figure 2.4: Role of anticancer drugs against various neurotoxins: Effect of neurotoxins such as amyloid-beta, glutamate, alpha-synuclein, nitric oxide and microglia in the progression of neurodegenerative diseases. The microglial cells induce glutamate toxicity which in turn causes reduced ATP synthesis and ROS-mediated oxidative stress. The Reactive nitrogen species induce nitric oxide release, which is a potent neurotoxin. The major NDDs are marked by abnormal protein aggregation, that in turn causes neurotoxicity and neuronal death. The combined effect of oxidative stress and mitochondrial dysfunction promotes synaptic dysfunction and neurodegeneration. The adverse consequences of oxidative stress and mitochondrial dysfunction also affects different cellular phenomenon in cancer such as DNA, RNA and Protein damage, abnormal cell proliferation, metastasis, chromosomal abnormalities and redox imbalance. Anticancer drugs (Highlighted in pink) reverse the effects of various neurotoxins and thus ameliorates neurotoxicity.

2.7 CHALLENGES ASSOCIATED WITH REPURPOSED ANTICANCER AGENTS

The potential of chemotherapeutics agents in the repurposing for NDDs has already been shown in the above sections, but drug resistance and toxicity are the major hurdles. Drug resistance is a significant issue in drug development for brain disorders. The two main problems associated with drug resistance in the brain are- the presence of physical barriers such as BBB and CSF barrier, and another is the presence of drug efflux transporters. P glycoprotein (Pgp) and Multidrug-resistant proteins (MRP) are the two transporters which limit the availability of any drug to the brain [268]–[271]. A study confirms the poor brain penetration of Imatinib due to the overexpression of Pgp. Other chemotherapeutics like paclitaxel, methotrexate, mitoxantrone, and 5-FU also have a restricted approach to the brain [272], [273]. Another aspect of being considered is the toxicity associated with anticancer agents. Several anticancer drugs are found to be related to neuronal damage [274]. Platinum-based drugs, vinca alkaloids, taxanes, epothilones, proteasome inhibitors, and immunomodulatory drugs are the primary six classes of antineoplastic resulting in chemotherapy-induced peripheral neuropathy(CIPN) [275]. Thalidomide, an anticancer drug gain attraction due to its neuroprotective role in AD. Depending upon the dose, it causes peripheral neuropathy in 25-75% of patients [276]. The antiangiogenic effect of thalidomide causes neuronal hypoxia and secondary ischemia, accompanied by irreversible neuronal damage [203], [277]. Paclitaxel, another promising antitumor agent, triggers neuroinflammation by inducing the production of pro-inflammatory cytokines [278]. A single high dose of paclitaxel results in sensory neuropathy 24-72 hrs after dose intake in 59-78% of patients [279]. Tyrosine kinase inhibitors, the most attractive class of prospective neuroprotectants, are also associated with neuropathy. Peripheral neuropathy has been reported with Imatinib [280]. A case study highlighted the link between Dasatinib and demyelinating peripheral neuropathy, possibly by immune-mediated problems [281].

2.8 DRUG REPURPOSING

In the recent past, drug repurposing has gained attention of pharmaceutical industry with about 25% of drug approvals correspond to repurposed drugs. The conventional drug discovery method was based on *de novo* identification of new molecular entities (NME). The process involves different stages such as preclinical study, safety review, clinical studies, FDA review and post-approval safety analysis. On contrary, drug repurposing has four different stages of development including compound identification, compound procurement, development followed by post-approval safety analysis. The idea of drug repurposing has been emerged identifying the concept of 'polypharmacology' where one drug belongs to multiple off-targets with multiple beneficial effects. However, the concept of polypharmacology should be defined separately from drug promiscuity where a drug is able to bind multiple therapeutic and non-therapeutic targets with both beneficial and adverse effects [282].

2.8.1 APPROACHES OF DRUG REPURPOSING

Drug repurposing has two widely used alternative approaches- first is computational or *in silico* approach and the other is experimental or activity-based approaches. The *in silico* approach exploits different bioinformatics tools and databases to virtually screen the drugs from huge chemical libraries. On the other hand, experiment-based a

pproach utilizes various *in vitro* or *in vivo* disease models to validate the therapeutic efficacy of the candidate drugs [283]. Recently, advanced computational approaches such as machine learning, artificial intelligence and complex-networks have been employed with the aim of identifying new therapeutic interventions. Structural-based virtual screening is the most common method of computational drug repurposing which involves exploration of novel interactions between the target and drugs accessed from large chemical libraries. Molecular docking and 3D-structural similarity are the two different

categories of virtual screening. Apart from virtual screening, ligand-based approaches such as pharmacophore modeling and quantitative structure-activity relationship (QSAR) methods can be applied. These approaches rely on the fact that structurally similar compounds show similar biological properties [284]. Additionally, network-based approaches are alos used to establish relations between drugs, disease and target proteins. The advancement of high-throughput technologies simplified the management of data that can be processes and analyzed using network-related approaches. In recent times, data integration methods such as multi-omics data integration methods have been developed for quick and efficient data management. The multi-omics methods are based on the fact that a pathological indication is a result of complex interaction between genome, transcriptome, proteome and metabolome and the integration of multiple omics data provides a deep knowledge of biological mechanisms associated with a disease [285]. The second alternative approach of drug repurposing is the validation of drugs against a target. The most common method is the phenotypic screening of multiple drug combinations in desired disease models [286]. The second method is the target-based approach where disease–related targets are identified and then large compound libraries are detected against the target. The shortlisted hits are then validated and characterized in different cell-based assays.

2.8.2 METHODOLOGIES OF DRUG REPUPOSING

Based on the toxicological, pharmacological and biological information of drugs, drug repurposing methods are classified in three different classes- drug based, target-based and disease-based.

(a) Drug-based approach: The drug-based repurposing is exploiting the idea of structural, biological, chemical, pharmaceutical and mechanistic activities of drugs. this method can be applied for drug repurposing when there is sufficient information available

for the mechanism of action of the drugs. The core fundamental is that if drug D1 and D2 have same mechanisms of actions and drug D1 is approved for indication I1 then drug D2 is a potent repurposed candidate for indication I1. This method exploits the principles of traditional drug pharmacology to identify the biological efficacy of drugs without any knowledge about their targets. The drug-based repurposing involves inferring drug-disease relationships based on direct inference, indirect inference or the integration of both aspects [287].

(b) Disease-based approach: this method of repurposing acquires available knowledge of the disease in question. In this case, disease-related information such as disease-specific genetic data, transcriptomic data, proteomic data and/or metabolomics data is collected. It also requires the construction of disease 0-realted networks to identify the pharmacological targets and pathways. The hypothesis is that if two indication I1 and I1 are sharing common genetic and molecular mechanisms and if Drug D is used to treat indication I1 then drug D can serve as a repurposed candidate for indication I2 [288].

(c) Target-based approach: The target-centric approach involves investigation of new target-disease associations. If a drug D is approved against a target T for indication I1 then the relationship of the target with I2 is identified and related with drug D. Although, the advent of high throughput screening methods identification of novel associations becomes easy, the success of this approach is rare as finding new target-disease association is not a frequent event.

The different methods and approaches of drug repurposing are presented in **Figure 2.5**

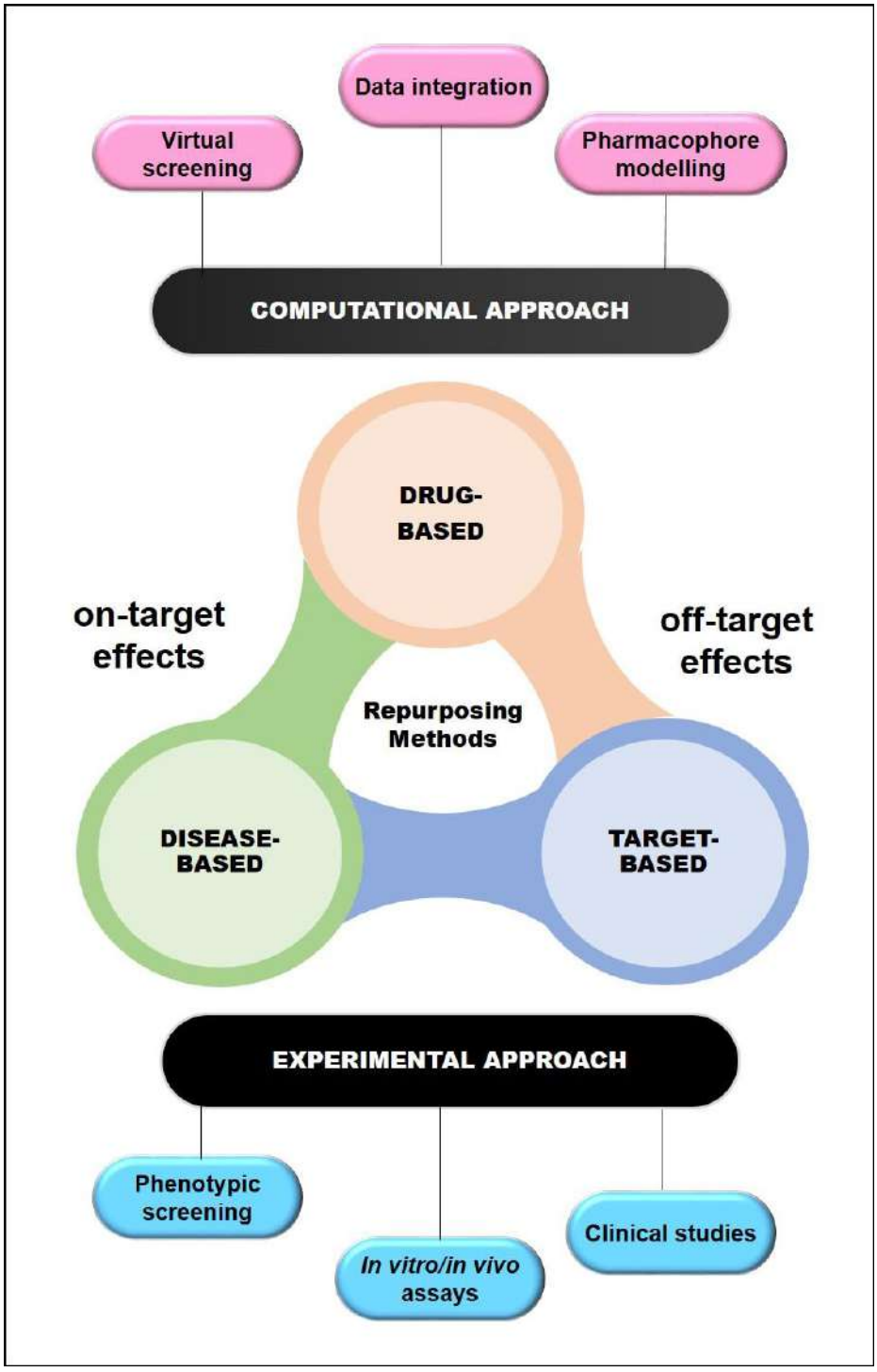


Figure 2.5: Methods and approaches used for drug repurposing. Three different methods are used for drug repurposing-Drug based, Disease-based and Target-based. The off- target or on-target effects are validated by using various computational and/or experimental methods.

2.9 NATURAL COMPOUNDS AS NEUROPROTECTANTS

Nature is a prolific source of structurally active metabolites that possess broad biological activities such as antimicrobial, antioxidant, anti-inflammatory and neuroprotective

activities. Till date, different classes on natural products including alkaloids, flavonoids, phenols, terpenes, alcohols, and many others. The high specificity and great affinity for biological targets advocate the potential of natural products in drug discovery and development [289]. In past years, there is a resurgence of natural products for drug repurposing of various NDDs. The natural products are known for their neuroprotective properties such as preventing oxidative stress, mitochondrial dysfunction, neuroinflammation, exitotoxicity, and neuronal apoptosis. Some of the selected natural compounds known for neuroprotective functions are summarized in **Table 2.4.**

Recently, technological advancements have made it possible to repurpose natural compounds by identification of new targets for natural compounds and their validation by computational and experimental approaches. Despite various promising functions as neuroprotectant, the translation of natural products from preclinical to clinical settings is still challenging. The poor bioavailability, reduced BBB permeability, chemical instability, rapid degradation, and reduced water solubility are the major concerns [290]. Thus, the area is still under investigation and new drug development strategies have to be discovered for utilizing the complete potential of natural compounds.

Table 2.4: Selected examples of the natural compounds with neuroprotective functions

Compound name	Model system	Neuroprotective functions	References
Agaricus blazei extract	Rotenone-induced PD mouse	Attenuation of oxidative stress by restoring the levels of free radical scavenging enzymes Promotion of dopamine synthesis by depleting the levels of tyrosine hydroxylase enzyme Inhibition of neuroinflammatory marker expression	[291]
Anthocyanin from strawberries	$hSOD1^{G93A}$ ALS mouse model	Reduction in astrogliosis Preserved neuromuscular activity	[292]
Boswellic acids	Rotenone-induced PD mouse	Amelioration of dopaminergic neurons degeneration Reduction in neuroinflammatory markers	[293]
Celastrol	APP/PS1 transgenic mice	Reduction in Aβ accumulation by decreasing beta-secretase levels Promotes heat shock response by activation of heat shock factor 1 (HSF1)	[294] [295]
Epigallocatechin	MPTP-induced PD mouse	Reduction in oxidative stress by regulating iron levels in substantia nigra	[296]
Huperzine A from Huperzia serrata	Double transgenic mouse Primary cortical neurons	Selective inhibition of acetylcholinesterase activity Reduction in the accumulation of Aβ42-induced neurotoxicity	[297] [298]
Ginkgo biloba extract	Transgenic mouse AD model	Reduction in synaptic dysfunction, amelioration of microglial activity and reduced neuroinflammation	[299]
Safflower yellow	AD mouse model	Reduction in hippocampal and cortical neuronal loss Suppression of glial cell activity Reduction in inflammatory markers such iNOS, IL-6, and TNF-α	[300]
Sulforaphane	AD-lesion mouse	Improved neurobehavioral symptoms, reduced lipid peroxidation and Aβ toxicity	[301]
Tribulus terrestris extract	Rotenone-induced PD mouse	Reduction in DNA damage markers, and suppression of oxidative stress by promoting superoxide dismutase and catalase activities	[302]

2.10 CHALLENGES ASSOCIATED WITH REPURPOSED ANTICANCER AGENTS

The goal of repurposing drugs for different NDDs is still challenging and several attempts have been failed due to the complex nature of these indications. Anticancer, antipsychotic, antidepressive, antihypertensive, antimicrobials, anti-asthma, and anti-diabetic drugs are the prominent classes of drugs that have been repurposed for NDDs. Drug resistance and toxicity are the major associated hurdles. Drug resistance is a significant issue in drug development for brain disorders. The two main problems associated with drug resistance in the brain are- the presence of physical barriers such as BBB and CSF barrier, and another is the presence of drug efflux transporters. P glycoprotein (Pgp) and Multidrug-resistant proteins (MRP) are the two transporters that limit the availability of any drug to the brain [268]–[271]. A study confirms the poor brain penetration of imatinib due to the overexpression of Pgp. Other chemotherapeutics like paclitaxel, methotrexate, mitoxantrone, and 5-FU also have a restricted approach to the brain [272], [273]. Another aspect is the toxicity associated with anticancer agents. Several anticancer drugs are found to be related to neuronal damage [274]. Platinum-based drugs, vinca alkaloids, taxanes, epothilones, proteasome inhibitors, and immunomodulatory drugs are the primary six classes of antineoplastic, resulting in chemotherapy-induced peripheral neuropathy (CIPN) [275]. Thalidomide, an anticancer drug, gain attraction due to its neuroprotective role in AD. Depending upon the dose, it causes peripheral neuropathy in 25-75% of patients [276]. The antiangiogenic effect of thalidomide causes neuronal hypoxia and secondary ischemia, accompanied by irreversible neuronal damage [203], [277]. One of the most devastating side effects of thalidomide is its teratogenic effect as the drug targets tissue-specific vessels, causing their loss through oxidative stress induction and causing severe embryopathy [303]. A study by Isidori et al. also highlighted the teratogenic effects of anticancer drugs

fluorouracil and imatinib in frog embryos where the drugs have shown adverse effects on embryogenesis and induced developmental malformations [304]. Paclitaxel, another promising antitumor agent, triggers neuroinflammation by inducing the production of pro-inflammatory cytokines [278]. A single high dose of paclitaxel results in sensory neuropathy 24-72 hrs after dose intake in 59-78% of patients [279]. Tyrosine kinase inhibitors, the most attractive class of prospective neuroprotectants, are also associated with neuropathy. Peripheral neuropathy has been reported with imatinib [280]. A case study highlighted the link between dasatinib and demyelinating peripheral neuropathy, possibly by immune-mediated problems [281].

Apart from neurological toxicities and neuropathies, several other long terms- and short-term side effects were reported with chemotherapeutics. A review by Rapoport et al. highlighted that chemotherapy-induced nausea and vomiting (CINV) is a frequently appearing and poorly controlled symptom associated with chemotherapy [305]. Nephrotoxicity, including hepatic dysfunction, obstructive jaundice, metabolic disturbances, glomerular injury with proteinuria, and acute kidney injury, is another complication associated with anticancer agents [306]. Many anticancer drugs such as methotrexate, imatinib, dasatinib, thalidomide, and nitrosoureas are found to be associated with pulmonary toxicities such as pulmonary embolism, pneumonitis, pleural effusions and pulmonary hypertension [307]. Drug-induced liver injury (DILI) is another challenging side effect of chemotherapy. Hepatic failure, steatosis, cirrhosis/fibrosis, disturbed drug metabolism are the identified symptoms accompanied with chemotherapy treatment. All the mentioned side effects and the associated clinical manifestations pose a challenge to repurpose anticancer drugs. Altogether, close monitoring of drug mechanism of action, evaluation of side effects, identification of effective drug dose are the prerequisite steps in the of repurposing of chemotherapeutic drugs

CHAPTER III

THERAPEUTIC TARGETING OF REPURPOSED ANTICANCER DRUGS IN ALZHEIMER'S AND PARKINSON'S DISEASE: USING THE MULTIOMICS APPROACH

CHAPTER III: THERAPEUTIC TARGETING OF REPURPOSED ANTICANCER DRUGS IN ALZHEIMER'S AND PARKINSON'S DISEASE: USING THE MULTIOMICS APPROACH

3.1 INTRODUCTION

The complexity and heterogeneity of multiple pathological features make AD and PD a major culprits to global health. Drug repurposing is an inexpensive and reliable approach to redirect the existing drugs for new indications. Herein, we aimed to study the possibility of repurposing approved anticancer drugs for AD and PD treatment. We adopted an integrated omics data-based repurposing strategy, including genomics, transcriptomics, and metabolomics, and validated our results by different computational methods. Our study is concentrated on FDA-approved anticancer drugs and their repurposing for AD and PD. We developed a bioinformatic pipeline to assign a ranking of the repurposed drugs based on the computational drug repurposing score (CoDReS) validated by network and structural similarity analysis with approved AD and PD drugs. The study also aims to combine the physicochemical analysis, drug-likeness, pathway analysis, and microRNA (miRNA) analysis of repurposing anticancer drugs to understand better the mechanisms involved. The study helped to identify the significant pathways and cancer-related genes associated with the pathogenesis of AD and PD. The study also set a new direction to understand the complex relationship between AD, PD and cancer that would be considered for other NDDs. Our computational drug repurposing approach proposed EGFR inhibitors as potential repurposing drugs for AD and PD. Consequently, our proposed framework could be used for drug repurposing for different indications in an economical and efficient way.

3.2 COMPUTATIONAL METHODS

3.2.1 DATA EXTRACTION

To obtain information on AD and PD-associated genetic variations, we analyzed GWAS studies for AD and PD from NHGRI-EBI GWAS Catalog (http://www.ebi.ac.uk/gwas) [308]. The database provides a consistent knowledge of single nucleotide polymorphism (SNP)-trait associations for various diseases. We extracted GWAS data for 1) PUBMED ID, 2) study accession, 3) genes, 5) SNPs, 6) P-value, and 7) OR (odds ratio). Genes are considered significant, which fall under the genomic regions associated with SNPs (r^2>0.6). For transcriptomics data, the NCBI Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) database that contains microarray and next-generation sequence functional genomic datasets [309] and the GEO RNA-seq Experiments Interactive Navigator (GREIN) database, which is an interactive platform for analysis of GEO RNA seq data [310] were used. The collected expression profile of the AD series GSE1297 was analyzed by GEO2R. The GSE1297 series contains microarray analysis data of the hippocampal region of 9 control and 22 AD subjects. GSE 136666 series for PD contains information of RNA sequencing data of 8 PD and 8 control patients from substantia nigra and putamen regions. The proteomics and metabolomics data were collected from the Human Metabolome Database (HMDB,http://www.hmdb.ca)[311] and UniProt Knowledgebase (UniProtKB, https://www.uniprot.org/) database [312]. The databases were searched for 1) AD and PD-linked metabolites, 2) protein name, 3) Uniprot ID, 4) type of metabolite and 5) gene name.

3.2.2 PRIORITIZATION OF CANDIDATE GENES

We utilized two different computational tools to identify the most significant genes associated with AD and PD. The genes obtained from various omics approaches were then subjected to enrichment analysis by online DAVID functional annotation tool and Gene set to Diseases (GS2D) tool. DAVID (https://david.ncifcrf.gov) provides an integrated

platform to extract meaningful biological information from the list of genes enriched in genome-scale studies [313]. GS2D (http://cbdm.uni-mainz.de/geneset2diseases) is a web tool that performs enrichment analysis based on significant biomedical citations from PubMed [314]. The gene-disease associations were filtered by a minimum number of citations found (default = 5), the minimum number of gene-disease associations (default =2), and the maximum false discovery rate (FDR=0.05). FDR is used as a matric in drug repurposing to measure significance of drug-indication scores [315].

The enriched genes were then analyzed for protein-protein interaction using the Molecular Interaction Search Tool (MIST) database. MIST (http://fgrtools.hms.harvard.edu/MIST/) database can be used to devise significant protein-protein and genetic interactions for different species [316].

3.2.3 DRUG TARGET MAPPING

We combined the information from genomics, transcriptomics, and metabolomics/proteomics approaches and had a list of genes associated with AD and PD. To develop a link between AD and PD-related genes with currently available drug projects, we tracked two different databases. DrugBank (www.drugbank.com) (version 5.1.5) contains around 13,554 drug entries incorporating various approved and experimental small molecules and biologics [317]. Similarly, the Therapeutic Target Database (TTD) (http://db.idrblab.net/ttd/) accommodates 3419 targets and 37316 drug projects [318]. We included only those targets for which anticancer drugs are available and excluded the others. All the drugs with clinical, experimental, or withdrawn status were excluded, and only FDA-approved drugs were considered for this study. The information about drugs like drug name, DrugBank ID, current indication, and drug mode of action was collected.

3.2.4 VALIDATION OF CANDIDATE DRUGS

The protein-protein interactions from the previous steps were then analyzed by the STRING database (string-db.org) which covers known and predicted interactions for different organisms [319]. The experimentally significant interactions (with high interaction scores) were selected, and the others were excluded from the study. The drug-target interactions were evaluated using the STITCH (Search tool for interactions of chemicals) (http://stitch.embl.de/) database that integrates interactions of 300,000 chemicals and 2.6 million proteins [320]. In a complex system, two interacting genes are represented as nodes connected by an edge. The interaction networks were further analyzed, and networks were generated by Cytoscape software v3.3.0 (www.cytoscape.org).

For validation of promising drug candidates on the validation network, we measured network topology parameters like degree centrality, betweenness, and topological coefficients by using the CentiScaPe app on Cytoscape software. A degree is a topological parameter corresponding to the number of interactions or connections for a given node. Betweenness corresponds to the centrality index of a given node. It represents the shortest path between two adjacent nodes. In biological networks, only a few nodes (hub nodes) have a high degree centrality and the nodes having the shortest path distance are designated as bottlenecks. Both hub nodes and bottlenecks are considered topologically important and biologically significant [321]. The topological coefficient is a relative measure that denotes the extent to which a node shares neighbors with other nodes in the network. The nodes that share no neighbor are assigned a topological coefficient value of 0. The candidate drugs were given ranks based on different topological parameters. The drugs having a higher degree centrality value were considered as topologically important and biologically

significant. In short, the drugs (nodes) with higher degree centrality values are regarded as hub nodes with considerable importance in the network.

3.2.5 DRUG REPURPOSING

The candidate drugs obtained from the previous studies were analyzed for their repurposing potential for AD and PD by using the CoDReS tool. CoDReS (http://bioinformatics.cing.ac.cy/codres) is a web-based tool that integrates information from the biologically available datasets, calculates affinity scores of protein and ligand pairs, evaluate drug-likeness and structural similarities [322]. The candidate drugs with good repositioning scores were then presented by the hierarchical clustering algorithm of the ChemMine server [323]. Hierarchical clustering is a powerful approach to finding structural and physicochemical similarities of compounds based on atom pair similarity measures. The similarity scores were calculated based on the Z-score values. Also, we calculated the structural similarity with the approved Alzheimer's drugs, namely-donepezil, rivastigmine, galantamine, and memantine and Parkinson's drugs- apomorphine, amantadine, benztropine, carbidopa, entacapone, istradefylline, levodopa, opicapone, pramipexole, rasagiline, ropinirole, rotigotine, safinamide, selegiline, tolcapone, and trihexyphenidyl. The similarity workbench tool of the ChemMine server was used, and similarity scores were represented as the Tanimoto coefficient, the most widely used metric to compare the molecular structure similarities in medicinal chemistry[324]. The tool utilizes the maximum common substructure (MCS) fingerprint method to find the largest substructures two compounds have in common and present it as the Tanimoto coefficient.

3.2.6 LITERATURE VALIDATION OF DRUG-DISEASE RELATIONSHIPS

To obtain the information related to neuroprotective functions of anticancer drugs, we have searched the PubMed database by using the keywords- "anticancer drugs and neuroprotection," "anticancer drugs and Alzheimer's disease," anticancer drugs and

neurodegenerative disorders", anticancer drugs and Parkinson's disease. We collected information on whether the proposed repurposing drugs have any neuroprotective mechanism associated with them.

3.2.7 DRUG-LIKENESS AND BBB PERMEABILITY ANALYSIS OF CANDIDATE DRUGS

The development of drugs for CNS disorders poses a challenge due to the BBB. While designing a drug for brain diseases, physicochemical properties and brain permeation properties should be optimized. Considering this challenge, we analyzed our candidate repurposed drugs for physicochemical properties using the SwissADME analysis tool. SwissADME (http://www.swissadme.ch/) is a user-friendly web tool to predict physiochemical properties, pharmacokinetics, and drug-likeness of small molecules [325]. We collected information about physiochemical properties as described in Lipinski's rule of five (RO5) like molecular weight, number of rotatable bonds, number of H-bond donors and acceptors present, partition coefficient (MlogP), and topological polar surface area (TPSA), where MlogP was the measure of lipophilicity and TPSA was the measure of the sum of the surfaces of polar atoms present.

3.2.8 FUNCTIONAL SIMILARITY ANALYSIS WITH micro-RNAs

To further validate our results, we identified miRNAs related to AD and PD from HMDD (Human microRNA Disease Database) (https://www.cuilab.cn/hmdd) [326]. HMDD contains information regarding experimentally validated microRNA-disease associations We also retrieved information of miRNAs associated with the identified repurposed drugs and then constructed a network that combines miRNAs that share common targets between the repurposed drugs and AD and PD. We considered only the miRNAs that were neuroprotective in nature. The disease-miRNA-drug and miRNA-drug relationships were

presented in the form of a network using Cytoscape software. The information of AD-related miRNAs, repurposed drugs, and their targets was given as input.

3.2.9 PATHWAY ANALYSIS

To discover the molecular mechanisms regulated by the identified genes, we performed pathway analysis (KEGG [327], Bioplanet [328], and WikiPathways [329]) by using the Enrichr tool. Enrichr (http://amp.pharm.mssm.edu/Enrichr/) is a web-based enrichment analysis tool that accumulates biological knowledge (genes, diseases, pathways, drugs) of more than 102 gene set libraries [330]. The tool has provided information about biologically relevant pathways or enriched pathways for the set of the given genes. These enriched pathways were associated with the given gene list more than would be expected by chance. We also extracted the information of disease signatures (DisGeNET and OMIM-based information) related to the given genes by using the Enrichr tool. The output of Enrichr is ranked list terms, and ranking is provided based on p-value scores. Enrichr calculates the p-value based on Fisher's exact test that assumes binomial distribution and independence for the probability of the given input gene.

An overview of the complete pipeline is shown in **Figure 3.1.**

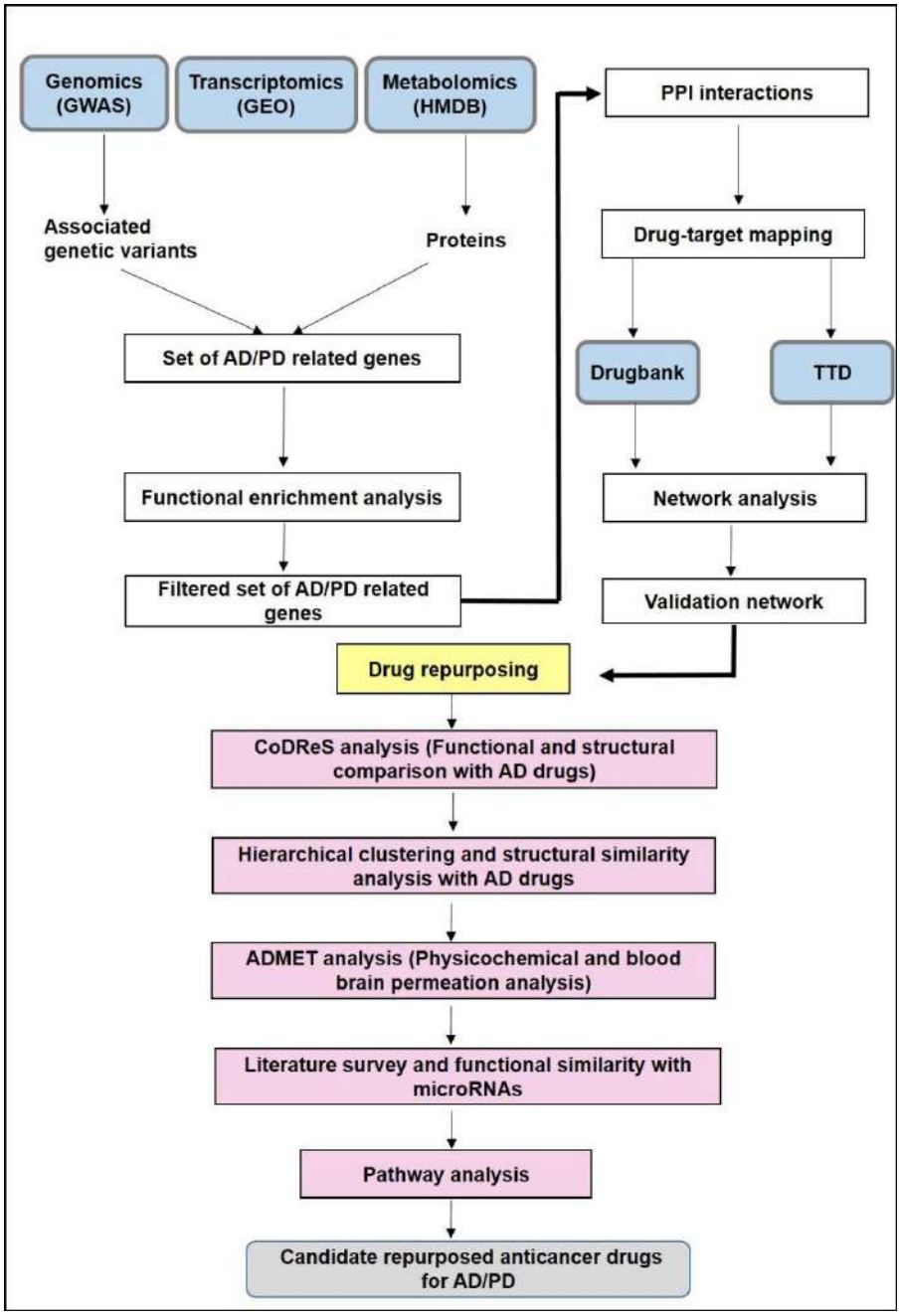


Figure 3.1: Flow chart of drug repurposing by omics data mining for Alzheimer's disease (AD) and Parkinson's disease (PD): We retrieved information on AD and PD risk genes from GWAS, transcriptomics and metabolomics approaches. After functional enrichment analysis, we filtered out AD and PD-associated targets. The PPI network analysis resulted in different PPI interactions. We performed drug target mapping to find candidate drugs from DrugBank and TTD databases. We excluded the information related to investigational and experimental drugs. We analyzed gene-gene and gene-drug interactions and selected the top PPI interactions that correspond to differnet anticancer compounds. These drugs were then analyzed by the CoDReS web tool that proposes potential candidate drugs for AD and PD. These drugs were then compared with the available AD and PD therapeutics for structural and functional similarities. ADMET analysis, pathway analysis and functional similarity with miRNAs resulted in potential repurposing anticancer drugs for AD and PD.

3.3 RESULTS

3.3.1 OMICS DATA MINING AND ENRICHMENT ANALYSIS REVEALED AD AND PD-RELATED GENES

The omics data approach enabled us to identify AD and PD-related genes. We collected information about 58 unique genes from 37 GWAS studies related to AD, while in case of 54 GWAS-related studies, 273 unique genes were found. Further, we identified 229 genes and 138 genes in the form of differentially coexpressed genes from transcriptomics study for AD and PD, respectively. Likewise, from metabolomics/proteomics analysis, 2627 AD-related genes and 188 PD-related genes were retrieved. We combined the information from different omics approaches, and finally, 2914 genes were found to be associated with AD while 580 genes were PD-specific.

DAVID functional enrichment analysis of 2914 genes revealed 212 genes have significant associations with AD. Similarly, G2D functional enrichment analysis revealed that 28 genes were significantly linked with AD. When we compared the two enrichment analysis methods, 49 AD-related genes were shared in the two enrichment methods. Similarly, for PD, DAVID functional enrichment analysis resulted in 16 genes while from G2D analysis 72 genes were obtained. The combination of the two enrichment methods gave us 54 PD-related genes. the complete list of AD and PD-related genes is provided in **Annexure 1**. The comparative analysis of the genes found from different omics layers is presented in **Figure 3.2.**

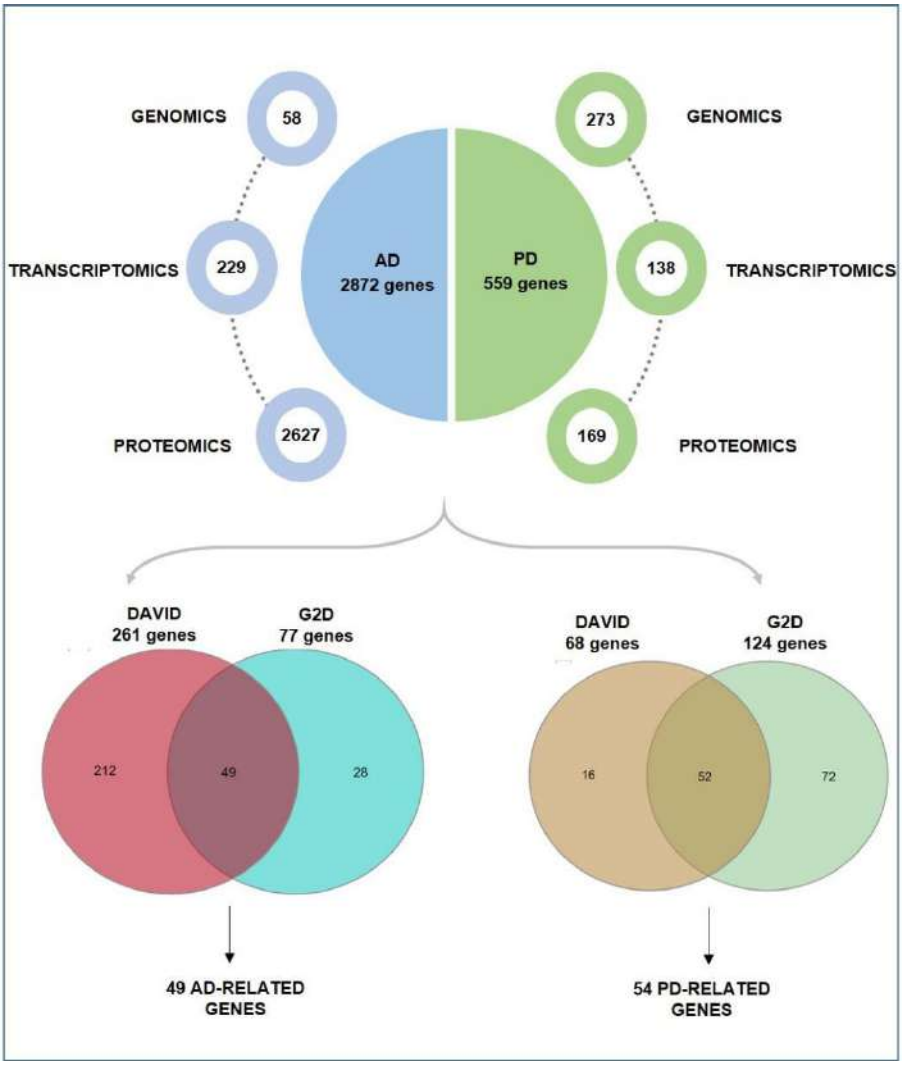


Figure 3.2: Representation of integrated omics (genomics, transcriptomics, and proteomics) analysis for AD and PD. After functional enrichment analysis, significant genes were identified for AD and PD

3.3.2 PPI NETWORK ANALYSIS REVEALED POTENTIAL INTERACTORS OF AD AND PD-RISK GENES

We evaluated the PPI network of the genes obtained from functional enrichment to explore the possibility of any of the genes from the PPI network serving as a target for approved anticancer drugs. We selected PPI interactions with a high confidence score and excluded the interactions with medium to low confidence. We found 828 PPI interactions for AD and 920 PPI interactions for PD, from the MIST database results, as shown in **Figure 3.3.** All the interactors in the network, along with AD and PD-risk genes, were searched in the DrugBank database and TTD to find the association with known anticancer drugs. The PPI

interactions were then evaluated by the STRING database and presented on the validation network. The topological parameters of genes in the STRING network, like degree centrality, betweenness, and topological coefficients, were analyzed by Cytoscape and presented in **Figure 3.4.**

The topological parameters were used to identify the hub nodes in the validation network. We identified glycogen synthase kinase beta (GSK3B), kinase insert domain receptor (KDR), amyloid precursor protein (APP), epidermal growth factor receptor (EGFR), and Fms-related receptor tyrosine kinase 1 (FLT1) as the top 5 nodes in AD network. GSK3B and KDR had the highest degree centrality values 4.0 and betweenness values 0.35, 0.32, respectively, while APP, EGFR, and FLT1 had degree centrality values 4 and betweenness values 0.69, 0.43, and 0.004, respectively. In the PD network, microtubule-associated protein tau (MAPT), leucine rich repeat kinase 2 (LRRK2), brain-derived neurotrophic factor (BDNF), Fyn proto-oncogene (FYN) and EGFR were selected as the top 5 nodes. MAPT and LRRK2 had the highest degree values 6 and 3, respectively with betweenness values 0.82 and 0. The nodes BDNF, FYN, and EGFR had degree centrality values 2 and betweenness values 0, 0.44 and 0.38, respectively.

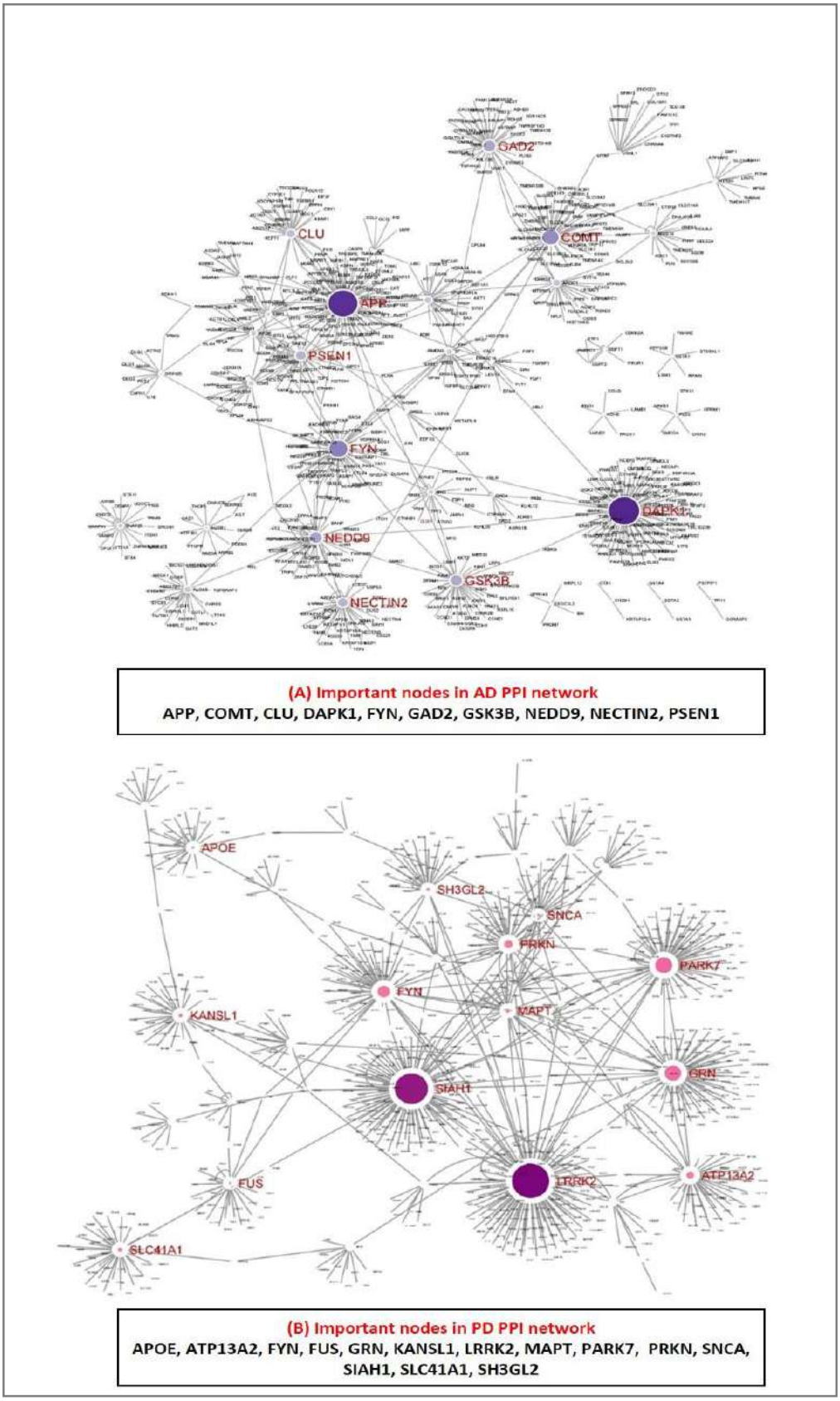
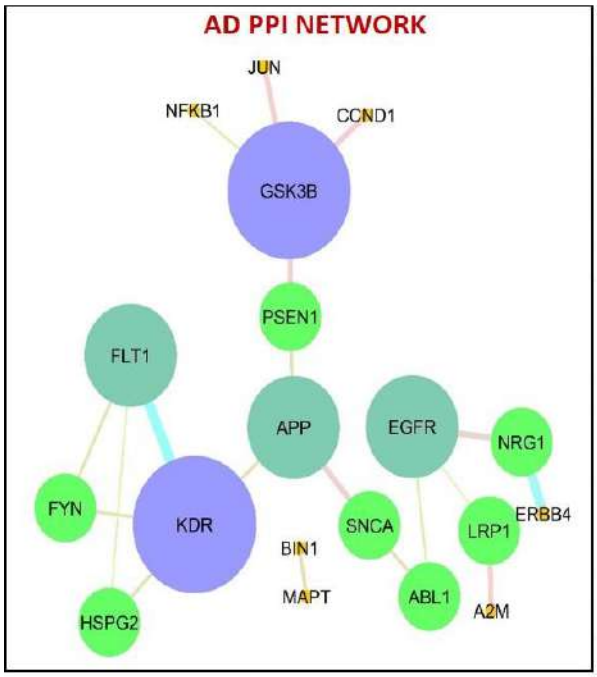


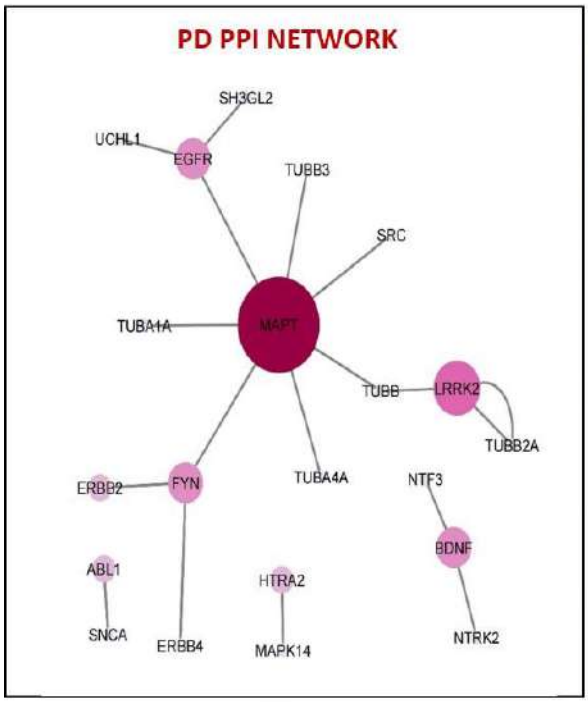
Figure 3.3: (A) The AD PPI network has 828 different interactions with 747 nodes. The important nodes are highlighted and presented in the boxes. (B) The PD PPI network has 920 different interactions with 831 nodes. The important nodes are highlighted and presented in the boxes.



(A)

Gene	Degree	Betweenness	Topological Coeff
GSK3B	4	0.35	0.25
KDR	4	0.329166667	0.45
APP	3	0.691666667	0.333333333
EGFR	3	0.433333333	0.333333333
FLT1	3	0.004166667	0.666666667
SNCA	2	0.5	0.5
ABL1	2	0.458333333	0.5
PSEN1	2	0.4	0.5
NRG1	2	0.125	0.5
LRP1	2	0.125	0.5
HSPG2	2	0	0.875
FYN	2	0	0.875
ERBB4	1	0	0
JUN	1	0	0
CCND1	1	0	0
A2M	1	0	0
MAPT	1	0	0
BIN1	1	0	0
NFKB1	1	0	0

(B)



(C)

Gene	Degree	Betweenness	Topological Coeff
MAPT	6	0.820512821	0.45
LRRK2	3	0	0.875
BDNF	2	0	0.875
FYN	2	0.448717949	0.5
EGFR	2	0.384615385	0.5
ERBB2	1	0	0
HTRA2	1	0	0
ABL1	1	0	0
NTF3	0	0	0
TUBB3	0	0	0
SH3GL2	0	0	0
SRC	0	0	0
TUBA4A	0	0	0
NTRK2	0	0	0
TUBB	0	0	0
TUBA1A	0	0	0
TUBB2A	0	0	0
MAPK14	0	0	0
SNCA	0	0	0
ERBB4	0	0	0
UCHL1	0	0	0

(D)

Figure 3.4: (A) and (B) STRING network of experimentally significant interactions for AD. Glycogen synthase kinase 3 beta (GSK3B), Vascular endothelial growth factor receptor 2 (KDR), amyloid precursor protein (APP), vascular endothelial growth factor receptor 1 (FLT1), and epidermal growth factor receptor (EGFR) were identified as the hub nodes with higest degree values in the network. (C) and (D) STRING network of experimentally significant interactions for PD. Microtubule-associated protein tau (MAPT), leucine rich repeat kinase 2 (LRRK2), brain-derived neurotrophic factor (BDNF), Fyn proto-oncogene (FYN), and EGFR were the hub nodes with the highest values for degree centrality.

3.3.3 DRUG MAPPING IDENTIFIED POTENTIAL REPURPOSING CANDIDATES FOR AD AND PD

First, we collected information of FDA-approved anticancer drugs by using DrugBank and TTD databases. The complete list of 172 approved drugs (excluding combinations and monoclonal antibodies) is provided in **Annexure 2**. Drug target mapping has shown that 28 direct PPI/AD-risk genes were associated with 36 FDA-approved anticancer drugs and 24 directPPI/PD-risk genes were associated with 44 FDA-approved anticancer drugs. We omitted the targets related to any investigational, experimental, or withdrawn anticancer drugs. The retrieved drugs were related to diverse modes of actions, like inhibitors, antagonists, substrates, and some had unknown functions. The experimentally significant interactions obtained from AD STRING analysis corresponded to 30 drugs from which 4 drugs (brigatinib, zanubrutinib, osimertinib, and erdafitinib) were not identified by the STITCH database and were excluded from the study. Of the 26 candidate repurposing drugs, 6 drugs (cisplatin, encorafenib, vinblastine, paclitaxel, docetaxel, and regorafenib) had not shown any interaction. Additionally, 3 drugs bosutinib, nilotinib, and dasatinib were in clinical trials for AD or related dementias and were not included in this study. Therefore, the remaining 17 drugs were considered novel candidates for repurposing for AD.

Likewise, for PD, the experimentally significant interactions were related to 33 drugs from which 7 drugs (brigatinib, larotrectinib, pralsetinib, zanubrutinib, tucatinib, umralisib and asciminib) were not identified by STITCH and were excluded from further analysis. Out of 26 drugs, only 15 anticancer drugs have shown interactions with significant PPI genes. Further, Nilotinib was removed from the study as it was in clinical trials for PD. Finally, we had selected 14 drugs for consecutive analysis. The summary of experimentally

significant AD/PD-related genes, their interacting PPI partners, associated drugs and the indications are presented in **Figure 3.5**

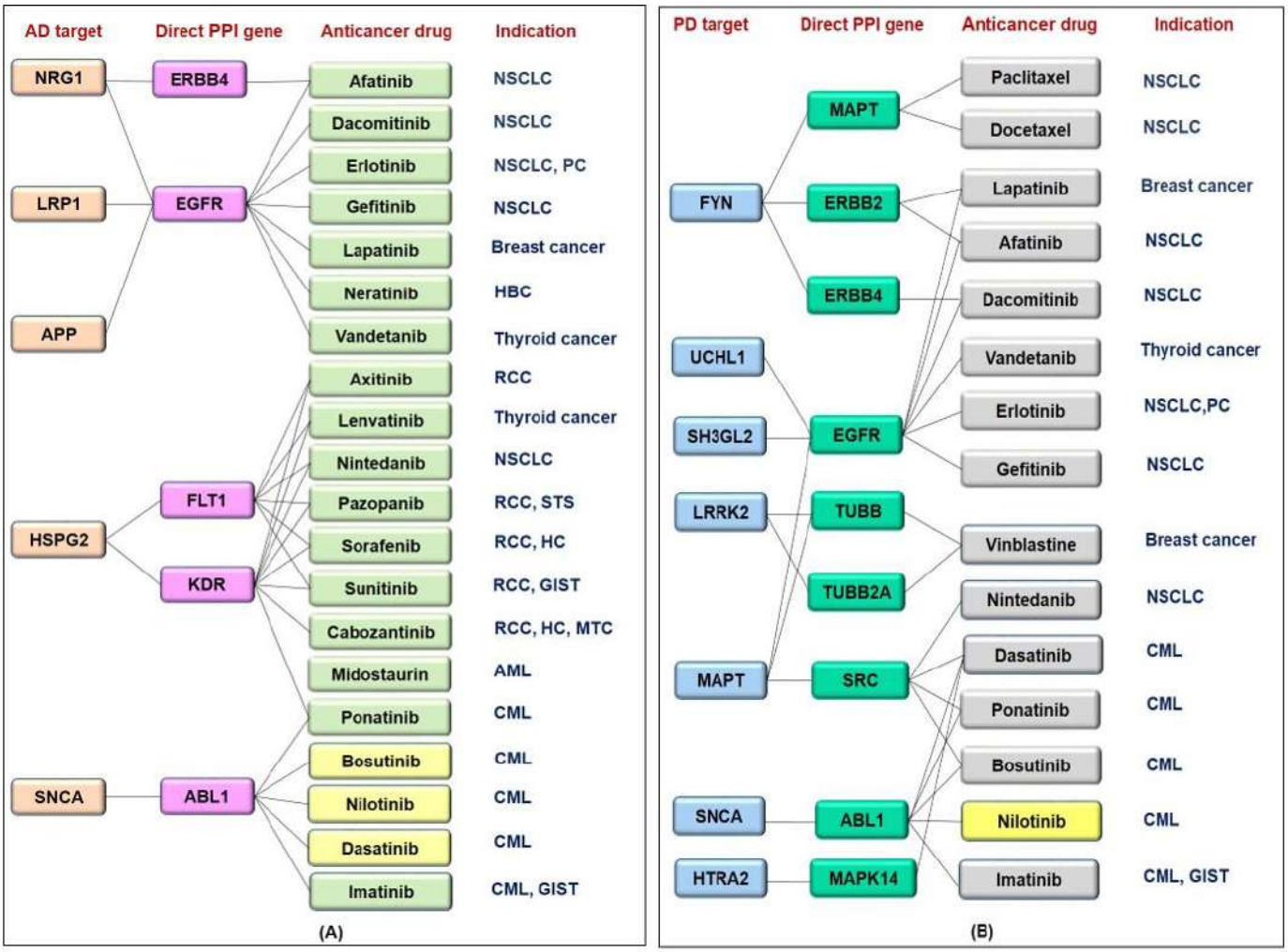
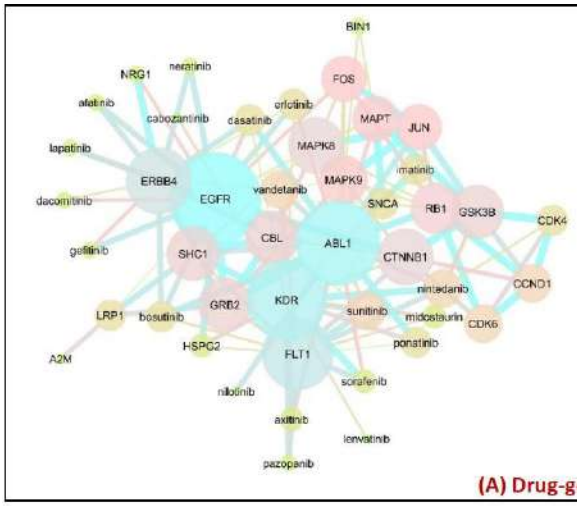


Figure 3.5: Summary of AD/PD risk genes, genes in direct PPI and targeted anticancer drugs. Drugs shown in yellow boxes were known in clinical studies as AD/PD therapeutics, and drugs in green and grey boxes were considered as potential repurposing candidates for AD and PD, respectively, NRG1: neuregulin 1; ERBB4: Erb-B2 receptor tyrosine kinase 4; LRP1: LDL receptor related protein 1; EGFR: epidermal growth factor receptor; HSPG2: heparan sulfate proteoglycan 2; FLT1: Fms related receptor tyrosine kinase 1; KDR: kinase insert domain receptor; SNCA: synuclein alpha; ABL1: ABL proto-oncogene 1, non-receptor tyrosine kinase, MAPT: microtubule-associated protein tau; FYN: Fyn proto-oncogene; UCHL1: ubiquitin C-terminal hydrolase L1; SH3GL2: SH3 domain containing GRB like protein 2; LRRK2: Leucine rich repeat kinase 2; TUBB: Tubulin beta class 1; TUBB2A: tubulin beta 2A class IIa; MAPK14: Mitogen activated protein kinase 14; HTRA2: Htr A serine peptidase 2; NSCLC: non-small cell lung cancer, PC: pancreatic cancer, HBC: HER-positive Breast cancer, RCC: renal cell carcinoma, STS: soft-tissue sarcoma, HC: hepatocellular carcinoma, GIST: gastrointestinal tumors, MTC: medullary thyroid cancer, AML: acute myelogenous leukemia, CML: chronic myelogenous leukemia

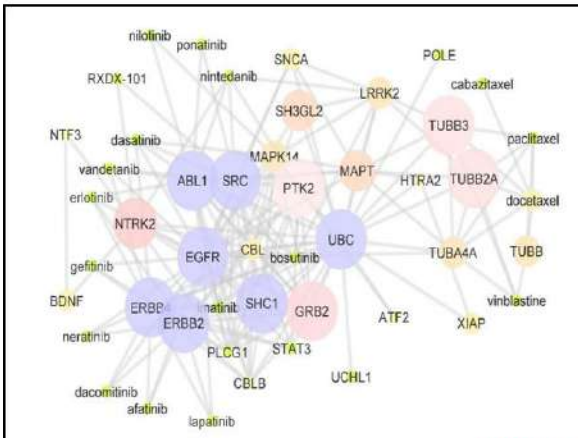
3.3.4 COMPUTATIONAL VALIDATION OF CANDIDATE REPURPOSED DRUGS

The drug-gene validation network was constructed using the STITCH database and analyzed by Cytoscape software, and drugs were ranked based on the degree centrality and betweenness values. The results shown in **Figure 3.6 (A)** have indicated that in drug-gene network for AD, nintedanib, sunitinib, and vandetanib were identified as the important hub nodes among promising drug candidates with a degree centrality of 5.0 and betweenness values 0.026, 0.021, and 0.011, respectively. We also identified the interactive targets of the topologically important drugs. The most considerable node nintedanib strongly correlated with the genes KDR, FLT1, GSK3B, cyclin-dependent kinase 4 (CDK4), and ABL proto-oncogene 1 (ABL1). Similarly, sunitinib interacted on the validation network with FLT1, KDR, EGFR, CDK6, and ABL1, while vandetanib had close interactions with ABL1, EGFR, KDR, and FLT1. The drug-gene network for PD in **Figure 3.6 (B)** has revealed that dasatinib, ponatinib, and bosutinib were the top 3 drugs with degree centrality of 4 and 2 with betweenness values 0.21 and 0.05, respectively. The drug with highest degree was dasatinib which has interactions with ABL1, SRC (Src proto-oncogene), erb-b2 receptor tyrosine kinase 4 (ERBB4) and mitogen-associated protein kinase 14 (MAPK14).



Rank	Drug name	Degree	Betweenness	Topological Coefficient
1	Nintedanib	5	0.026	0.44
2	Sunitinib	5	0.021	0.402
3	Vandetanib	5	0.011	0.482
4	Dasatinib	4	0.007	0.502
5	Erlotinib	4	0.007	0.502
5	Imatinib	4	0.006	0.548
6	Ponatinib	4	0.006	0.543
6	Bosutinib	4	0.004	0.513
7	Axitinib	3	0.002	0.679
7	Sorafenib	3	0.002	0.679
7	Midostaurin	3	0.002	0.597

(A) Drug-gene network for AD



Rank	Drug name	Degree	Betweenness	Topological Coefficient
1	Dasatinib	4	0.218974359	0.3125
2	Ponatinib	2	0.059487179	0.642857143
2	Bosutinib	2	0.059487179	0.642857143
2	Afatinib	2	0.070769231	0.555555556
2	Lapatinib	2	0.070769231	0.555555556
2	Dacomitinib	2	0.1	0.5
2	Vinblastine	2	0.036923077	0.75
3	Gefitinib	1	0	0
3	Erlotinib	1	0	0
3	Vandetanib	1	0	0

(B) Drug-gene network for PD

Figure 3.6: STITCH network for (A) Alzheimer's and (B) Parkinson's Disease. The drugs with highest values for degree centrality are selected. The highest value of degree is 5 for AD-related drugs while the highest degree is 4 for PD-related drugs.

Functional classification of drugs retrieved from the STITCH network has revealed that kinase inhibitors are the major class of anticancer drugs associated with AD and PD both. (**Figure 3.7**).

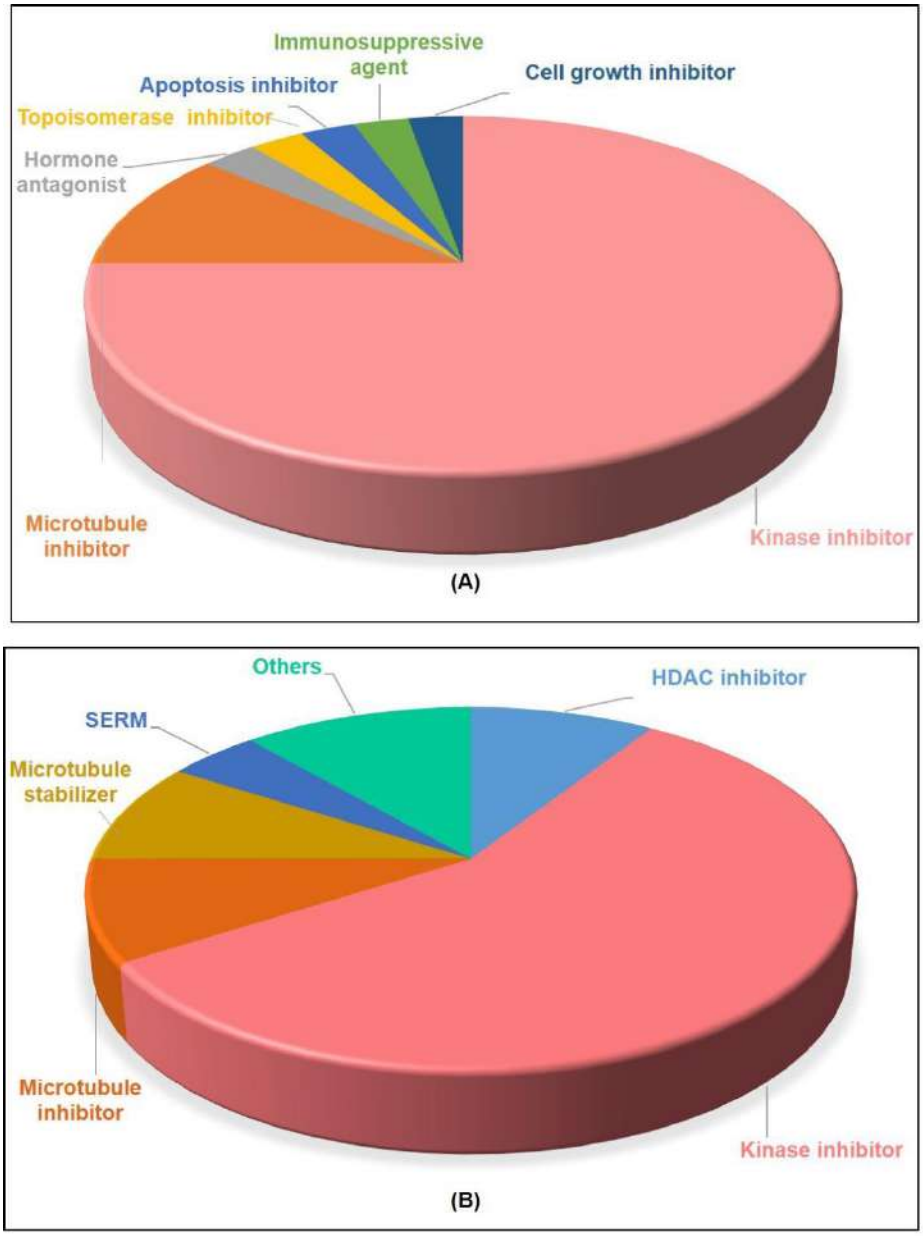


Figure 3.7: (A) and (B) Shows functional classification of candidate repurposing anticancer drugs for AD and PD. Kinase inhibitors followed by microtubule inhibitors are the most prevalent drugs having neuroprotective functions

3.3.5 FUNCTIONAL AND STRUCTURAL ANALYSIS VALIDATED THE REPURPOSING POTENTIAL OF CANDIDATE DRUGS

The potential repurposing candidates from the previous steps were evaluated for their functional and structural properties by the CoDReS tool. The tool is based on a disease-specific approach to compare drug-disease relationships concerning a training set of drugs

approved or investigated for a disease. We have incorporated this tool to re-rank the candidate drugs based on their repurposing scores. **Figure 3.8** illustrates the comparative functional, structural, and CoDReS scores of the candidate drugs, respectively. The values have suggested that most of the drugs have good structural scores, but functional scores have shown significant variations. We found that for AD, erlotinib had the highest functional score (1.0) while dacomitinib had the lowest value (0.001). Similarly, sunitinib, sorafenib, imatinib, gefitinib, vandetanib, lenvatinib, pazopanib, axitinib, afatinib, dacomitinib had the highest values (1.0) in terms of structural score, and lapatinib had the lowest score (0.33). Moreover, erlotinib had the highest CoDReS value (1.0), and lapatinib had the lowest (0.20). We have selected the top 10 drugs with the highest CoDReS scores for further study. The CoDReS results have indicated that erlotinib would be a good repurposing drug for AD having the highest functional and structural scores. Similarly, for PD, three drugs erlotinib, gefitinib, and vandetanib had good functional scores. The structural drugs had more or less similar values except for Lapatinib and Neratinib. Finally, we selected three drugs erlotinib, gefitinib and vandetanib based on CoDReS scores.

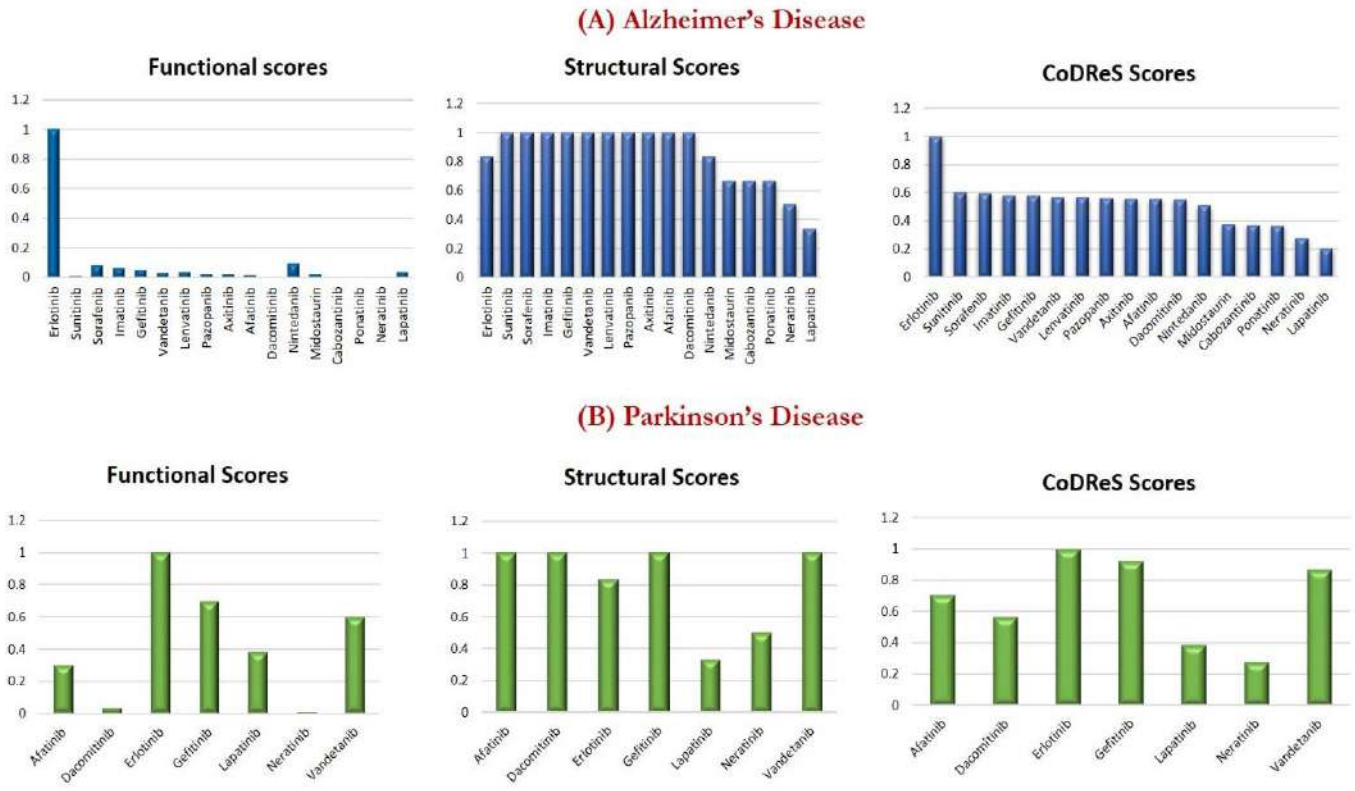


Figure 3.8: (A) The functional, structural and CoDReS scores of different candidate repurposing drugs for AD as calculated by CoDReS tool. Erlotinib, sunitinib, sorafenib, imatinib, gefitinib, vandetanib, lenvatinib, pazopanib, axitinib, afatinib, dacomitinib, and nintedanib were selected as repurposed drugs for AD based on the combined scores (B) The functional, structural and CoDReS scores of different candidate repurposing drugs for PD as calculated by CoDReS tool. Afatinib, dacomitinib, erlotinib, gefitinib, and vandetanib were selected for PD based on combined repurposing scores.

Additionally, we exploited the ChemMine server to investigate anti-Alzheimer's properties of candidate drugs and compared their clinical potential with four drugs approved for AD**.** The hierarchical clustering was performed using a clustering threshold of 1. We noticed no drug clusters with typical anti-Alzheimer drugs. We have selected the closest neighbors to donepezil like vandetanib, gefitinib, erlotinib, imatinib, afatinib, and sunitinib. Similarly, for another anti-Alzheimer's drug rivastigmine, we found sunitinib as the closest match. Likewise, for galantamine, we found vandetanib, erlotinib, gefitinib as the closest neighbor. We have found no nearest neighbor to memantine. For PD, similarity analysis has been performed with sixteen approved PD drugs. The list of approved drugs for AD and PD is provided in **Annexure 3**. The results are presented in **Figure 3.9**. We found

that only three drugs erlotinib, gefitinib and vandetanib were having some structural similarities with PD drugs. Erlotinib was found to be structurally similar to eight PD drugs, gefitinib was similar to six PD drugs while vandetanib was similar to four PD drugs.

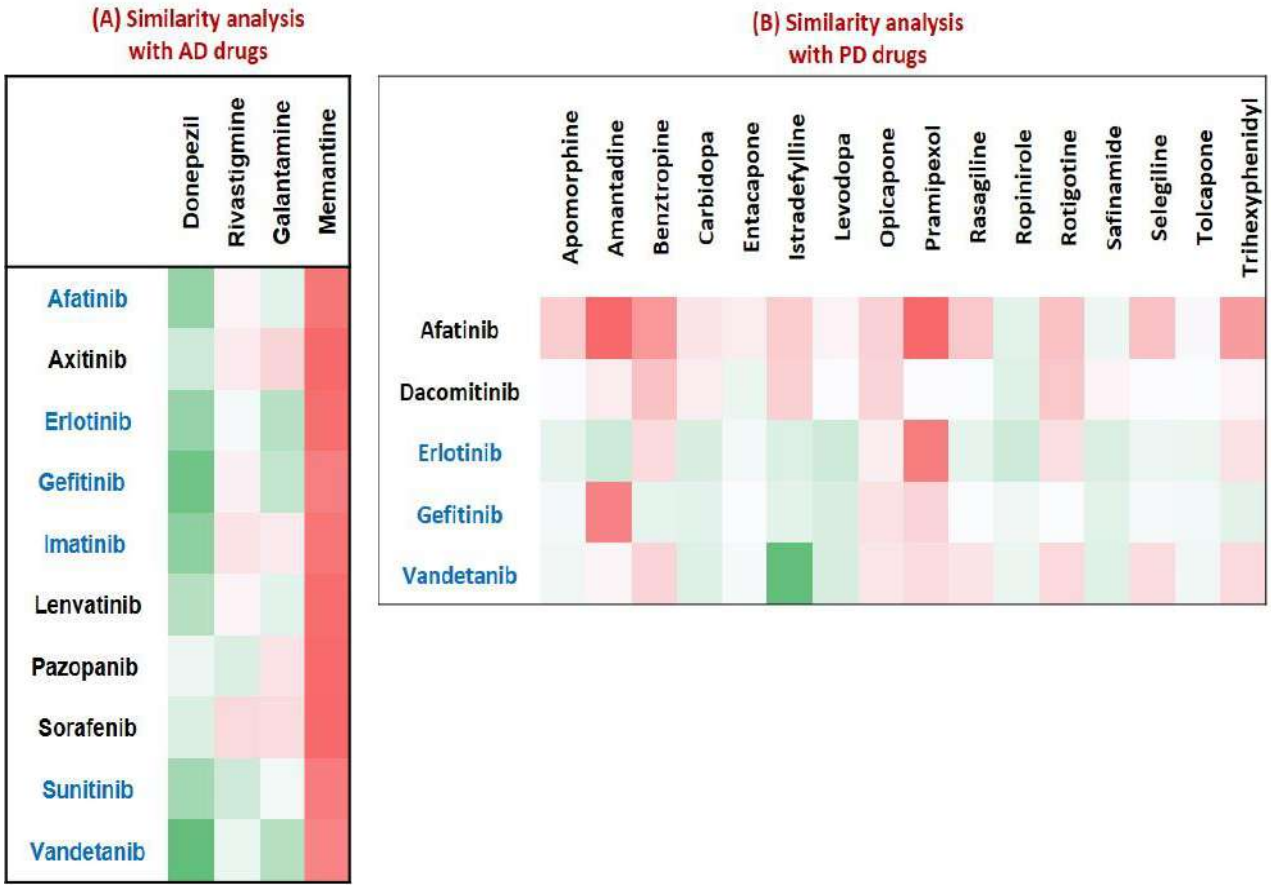


Figure 3.9: (A) Similarity analysis (based on Tanimoto coefficient) of repurposed drugs with known Alzheimer's drugs and (B) Parkinson'drugs. The drugs highlighted in blue had shown structural similarities. Drugs presented on Y-axis are anticancer drugs and presented on X-axis are AD/PD drugs

3.3.6 LITERATURE STUDIES, BBB PERMEABILITY AND DRUG-LIKENESS ANALYSIS CONFIRMED THE REPURPOSING POTENTIAL OF REPURPOSED DRUGS

To further validate our results, we have searched for the available information regarding the neuroprotective properties of the drugs proposed in the previous steps. A few bibliographic studies were available regarding the neuroprotective functions of anticancer drugs, as summarized in **Table 3.1.**

Table 3.1: Literature studies for neuroprotective functions of potential repurposing candidates

Drug	Neuroprotective function	References
Afatinib	Inhibition of oxygen/glucose-induced neuroinflammation and EGFR activation	[331]
Erlotinib	Reduction in Aβ-induced memory loss in AD	[332]
Gefitinib	Improvement in cognition and memory functions	[332]
	May improve AD pathogenesis by inhibiting the β-secretase activity	[333]
	Promotes PINK1/Parkin-mediated mitophagy by optineurin (OPTN)	[334]
Imatinib	Inhibition of Aβ accumulation by the selective inhibition of BACE activity	[213]
	Promotes degradation of Aβ by inducing the activity of Aβ-degrading enzyme neprilysin	[335]
	Inhibition of brain c-Abl, reduction in circulating levels of Aβ, shifts APP processing to non-amyloidogenic pathway	[336]
	Presents antiparkinsonian effects in MPTP PD mouse model	[337]
Sunitinib	Provides neuroprotection by inhibiting NO production	[215]
	Inhibition of Acetylcholinesterase activity and attenuation of cognitive impairments in scopolamine-induced AD mice	[338]
Vandetanib	May inhibit Acetylcholinesterase activity in AD	[339]

The drug-likeness analysis of the six drugs has confirmed that four drugs (erlotinib, gefitinib, vandetanib, and sunitinib) have good physicochemical properties (molecular weight, no of rotatable bonds, no of H-bond donors, no of H-bond acceptors, TPSA, and M log P) and were able to cross BBB, as shown in **(Annexure 4)**. Two drugs, afatinib and imatinib, would not be able to cross BBB and thus be excluded from the study.

3.3.7 FUNCTIONAL SIMILARITY ANALYSIS WITH microRNAS

To further validate our results, we extracted the list of AD and PD-related miRNAs and also searched for the miRNAs related to the repurposed drugs **(Figure 3.10 & Figure 3.11).** After comparison, we found that erlotinib and gefitinib shared three miRNAs with AD where only one miRNA has neuroprotective functions while vandetanib shared 33 different miRNAs with AD, of which 11 miRNAs have neuroprotective functions. We found that miRNA-200a is the only AD-related miRNA with a neuroprotective function associated

with all three drugs. miRNA-200a targets the EGFR gene, and a literature survey has confirmed its neuroprotective role in attenuating amyloid beta overproduction by downregulating BACE1 expression and tau hyperphosphorylation by reducing the expression of protein kinase A (PKA) [340].

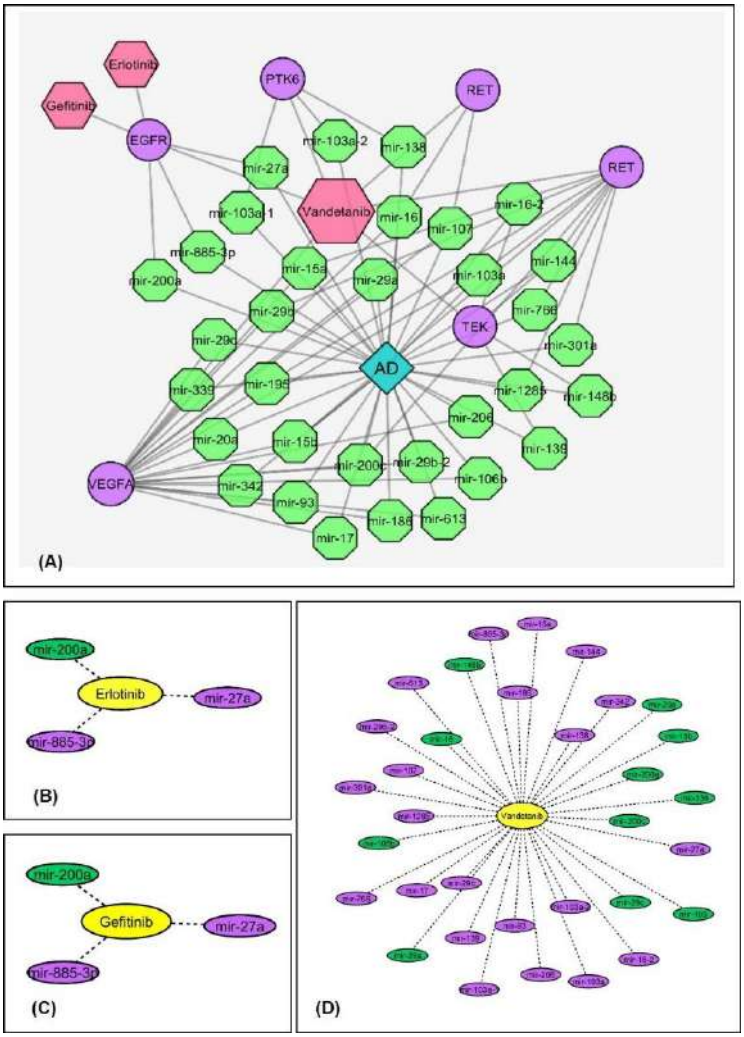


Figure 3.10: (A) Network is showing the interrelationship of miRNAs associated with AD and those associated with repurposed anticancer drugs- erlotinib, gefitinib, and vandetanib. The network shows vandetanib share many common targets such as EGFR, PTK6, RET, TEK, and VEGFA with AD-related miRNAs while both erlotinib and gefitinib share functional similarity through EGFR gene. (B-D) shows association of erlotinib, gefitinb, and vandetanib with miRNAs, respectively, where miRNAs shown in green are neuroprotective while miRNAs shown in purple are neurodegenerative as identified through literature analysis. miRNA-200a is the only one that shows association with all three repurposed drugs.

Likewise, for PD, we found that erlotinib shared 15 different miRNAs with PD out of which three miRNAs had neuroprotective functions. Gefitinib shared 7 different miRNAs of which 2 were neuroprotective and vandetanib shared 18 different miRNAs of which 3 were

neuroprotective. We also observed that miRNA-409 and miRNA-7-3 were the neuroprotective miRNAs interacting with all three drugs. A study by Tan et al. demostrated that miR-409 plays an essential role in PD by targeting ATXN3 (Ataxin3), an important player in mitochondrial autophagy and apoptosis [341]. In the same manner, a study by Choi et al. revealed that miR-7 binds to the synuclein alpha (SNCA) gene, thereby promoting alpha-synuclein degradation and clearance from the brain. Further, it supports dopaminergic neuronal survival in the substanita nigra [342].

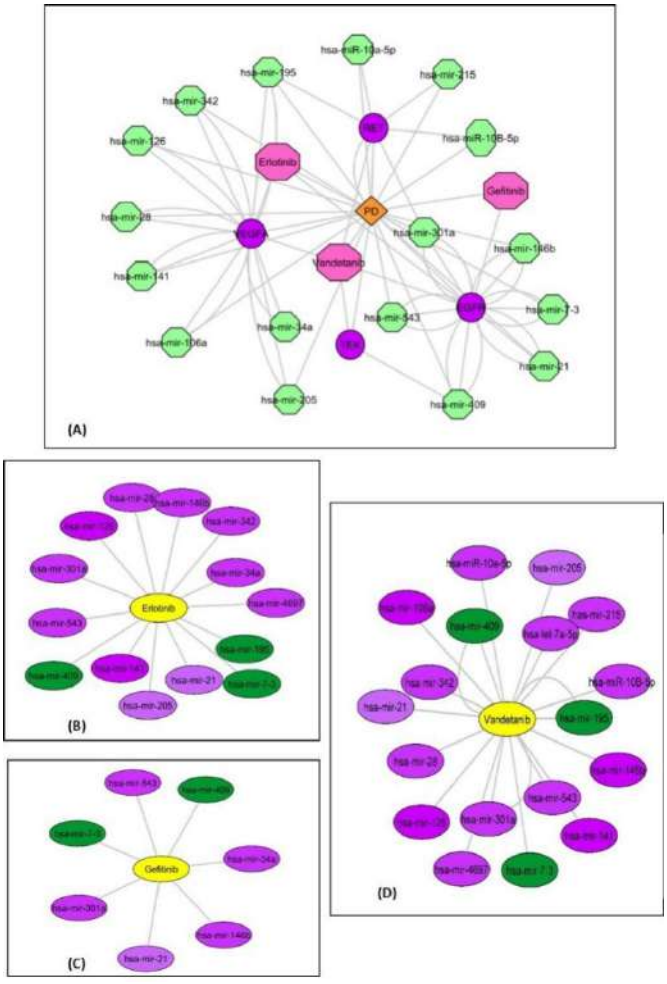


Figure 3.11: (A) Network shows the interrelationship of miRNAs associated with PD and those associated with repurposed anticancer drugs- erlotinib, gefitinib, and vandetanib. The network shows vandetanib share many common targets such as EGFR, PTK6, RET, TEK, and VEGFA with AD-related miRNAs while both erlotinib and gefitinib share functional similarity through EGFR gene. (B-D) shows association of erlotinib, gefitinb, and vandetanib with miRNAs, respectively, where miRNAs shown in green are neuroprotective while miRNAs shown in purple are neurodegenerative as identified through literature analysis. miRNA-409 and miRNA-7-3 are having associations with all three repurposed drugs.

3.3.8 PATHWAY ANALYSIS CONFIRMED THE REPURPOSING POTENTIAL OF EGFR INHIBITORS

The significant AD and PD-related genes were considered for pathway analysis by the Enrichr tool. We used KEGG, BioPlanet and WikiPathway databases for pathway analysis **(Table 3.2**). The most frequently appeared genes in the enriched pathways (biologically relevant) for AD were- EGFR, JUN and GSK3B. ERBb signaling pathway, focal adhesion, mitogen-activated protein kinase (MAPK) signaling, Cu homeostasis and PI3-Akt pathways were the top signaling pathways associated with AD pathogenesis. Many pieces of evidence are available for the pathways identified by our study with AD. The pathological role of ErBb4 activity in AD is confirmed by Woo et al., where ErBb4 was accompanied by AD progression [343]. The role of focal adhesion signaling in AD pathology is established because Aβ upregulates many proteins related to focal adhesion signaling that induce re-entry of neurons into the cell cycle [344]. Aberrant activation of focal adhesion kinases is associated with synaptic loss and neuronal dystrophy in AD [345]. Many studies have proposed that MAPK signaling plays an essential role in AD pathogenesis by regulating tau phosphorylation, APP processing, and neuronal apoptosis [125]. Several MAPKs interact with AD-related proteins such as tau, APP, Presenilin (PS), and Apolipoprotein E (ApoE) [346]. The role of Cu in AD pathogenesis is controversial. Some studies have demonstrated that Cu overload is responsible for neurotoxicity in AD brains, while other studies have proposed Cu deficiency as a contributing factor to AD pathogenesis [347]. Likewise, the role of the PI3K pathway is confirmed by studies where abnormal activities of the pathway were responsible for Aβ production and sequestration [348]. The PI3K pathway activation has therapeutic potential to treat AD as some of the drugs such as donepezil, coenzyme Q10, and human telomerase reverse transcriptase (hTERT) are known to treat AD by GSK3B inhibition and PI3K activation [349].

Table 3.2: Pathway analysis of STRING interactions based on p-values

S.No.	Pathway name	Genes involved	P-value**
ALZHEIMER'S DISEASE			
KEGG pathway analysis			
1	ErBb signaling pathway	GSK3B,JUN,ERBB4,ABL1,NRG1,EGFR	2.39E-11
2	Focal adhesion	GSK3B,JUN,FLT1,CCND1,KDR,EGFR	4.18E-11
3	MAPK signaling pathway	MAPT,JUN,FLT1,ERBB4,KDR,EGFR	4.38E-11
BioPlanet pathway analysis			
1	ErBb signaling pathway	GSK3B, JUN, CCND1, ERBB4, ABL1, NRG1,EGFR	2.52E-13
2	Focal adhesion	GSK3B, JUN, CCND1, FLT1, KDR, EGFR	1.08E-08
3	PI3-Akt pathway	GSK3B, ERBB4, NRG1, EGFR	2.73E-08
WikiPathway analysis			
1	ErBb signaling pathway	GSK3B, JUN, CCND1, ERBB4, ABL1, NRG1,EGFR	1.99E-13
2	Cu homeostasis	APP, GSK3B, JUN, CCND1, MAPT	2.87E-10
3	Focal adhesion	JUN, GSK3B, FLT1, CCND1, KDR, EGFR	4.06E-09
PARKINSON'S DISEASE			
KEGG pathway analysis			
1	Pathways of neurodegeneration	UCHL1, TUBA1A, TUBB2A, TUBB3, BDNF, LRRK2, TUBB, HTRA2,MAPT,MAPK14,EGFR, TUBA4A,SNCA	3.53E-13
---2	Parkinson disease	UCHL1, TUBA1A, TUBB2A, TUBB3, LRRK2, TUBB, HTRA2, MAPT, TUBA4A,SNCA	5.23E-13
3	Pathogenic Escherichia coli infection	TUBA1A, TUBB2A, SRC, TUBB3, TUBB, ABL1, FYN, MAPK14, TUBA4A	2.92E-12
BioPlanet pathway analysis			
1	Gap junction pathway	TUBA1A, TUBB2A, SRC, TUBB3,TUBB,EGFR,TUBA4A	2.43E-11
2	Post-translational regulation of adherens junction	NTRK2, SRC, BDNF, ABL1, FYN, EGFR	3.94E-11
3	EGF/EGFR signaling pathway	TNK2, ERBB2, ABL1, MAPK14, EGFR, SH3GL2	2.89E-08
WikiPathway analysis			
1	Parkin-Ubiquitin Proteasomal System pathway WP2359	TUBA1A, TUBB2A, TUBB3, TUBB, SIAH1, TUBA4A, SNCA	3.97E-12
2	BDNF signaling pathway WP2380	NTRK2, SRC, BDNF, NTF3, FYN, MAPT, MAPK14	6.82E-10
3	Parkinson's disease pathway WP2371	UCHL1, LRRK2, HTRA2, MAPK14, SNCA	1.47E-09

***Genes in red are the most frequently appeared genes in the enriched pathways**

Pathway analysis of PD-related genes demonstrated that EGFR, SRC, SNCA, TUBA1A, TUBB2A, TUBA4A, and TUBB3 frequently appeared genes in the enriched pathways. We identified that neurodegeneration, gap junction, post-translational regulation of adherens

junction, parkin-ubiquitin proteasomal System, and BDNF signaling were the significant pathways associated with PD pathogenesis. The adherens junction pathway is known to contribute maintaining BBB integrity and changes in this activity leads to BBB disruption in different NDDs, including PD [350]. A recently published study has highlighted the significance of structural and functional alterations in gap junctions and related connexins in PD pathogenesis [351]. The role of parkin-UPS system is well known in PD as parkin is the major role player in regulating the activities of α-syn, PINK1 and DJ1 and alterations in parkin activity are the major cause of autosomal recessive PD [352]. Likewise, BDNF is considered as a neuroprotectant and it supports dopaminergic neuron survival, improves neurotransmission and alleviates motor deficits in PD brains [353].

Table 3.3: Disease-based analysis of STRING interactions based on p-values

S.No.	Disease name	Genes involved	P-value
ALZHEIMER'S DISEASE			
DisGeNET analysis			
1	Amyloidosis	APP, BIN1, EGFR, ERBB4, FLT1, GSK3B, HSPG2, LRP1,MAPT,NRG1,SNCA	7.19E-13
2	Melanoma	ABL1, APP, BIN1, CCND1, EGFR, ERBB4, FLT1, GSK3B, HSPG2,JUN, KDR, LRP1, NRG1, SNCA	2.26E-12
3	Alzheimer's Disease	ABL1, APP, BIN1, CCND1, EGFR, ERBB4, GSK3B, HSPG2, JUN,LRP1,MAPT,NRG1,SNCA	7.44E-12
4	Central Neuroblastoma	APP, BIN1, CCND1, EGFR, ERBB4, FLT1, GSK3B, JUN, KDR, LRP1, MAPT, SNCA	3.57E-11
5	Non-small cancer lung carcinoma	ABL1, APP, BIN1, CCND1, EGFR, ERBB4, FLT1, GSK3B, JUN, KDR,LRP1, NRG1, SNCA	3.63E-11
OMIM disease analysis			
1	Dementia	APP, CCND1, EGFR, MAPT, SNCA	4.52E-09
2	Parkinson's Disease	CCND1, EGFR, MAPT, SNCA	7.39E-07
3	Alzheimer's Disease	APP, CCND1, EGFR	5.77E-05
4	Schizophrenia	CCND1,EGFR, NRG1	6.46E-05
5	Myopathy	BIN1, CCND1, EGFR	9.09E-05
PARKINSON'S DISEASE			
DisGeNET analysis			
1	Neurodegenerative disorders	BDNF, LRRK2, HTRA2, EGFR, HDAC6, ESR2, UCHL1, ERBB4, ERBB2, NTF3, ABL1, FYN, APOE, MAPT, SNCA	3.68E-15
2	Parkinson's Disease	BDNF, LRRK2, TNK2, SIAH1, HTRA2, MAPK14, ESR2,UCHL1,TUBA1A,NTF3,ABL1, EGFR, FYN, APOE, MAPT, SH3GL2, SNCA	2.76E-14
3	Lewy Body Disease	NTRK2, UCHL1, BDNF, LRRK2, HTRA2, FYN,APOE, MAPT,SNCA	8.18E-14

4	Amyloidosis	NTRK2, BDNF, LRRK2, MAPK14, EGFR, HDAC6, ESR2, UCHL1, ERBB4, ERBB2, NTF3, APOE, MAPT, SNCA	5.14E-13
5	Parkinsonian Disorders	UCHL1, BDNF, LRRK2, ABL1, HTRA2, FYN, APOE, MAPT, SNCA, EGFR	6.16E-12
OMIM disease analysis			
1	Parkinson's Disease	UCHL1, LRRK2, HTRA2, MAPT, SNCA	7.85E-11
2	Dementia	MAPT,SNCA	1.15E-04
3	Gastric cancer	ERBB2	0.014753703
4	Ovarian cancer	ERBB2	0.017413588
5	Myocardial infarction	APOE	0.021390456

*** Highlighted rows represent AD and PD-related genes**

DisGeNET and OMIM databases were used to find the most closely associated diseases with the identified genes **(Table 3.3).** For AD, the DisGeNET results reported that out of 15 genes, 13 genes were associated with AD (P-value- 7.44E-12), while OMIM disease analysis identified 3 genes (P-value- 5.77e-05) related to AD. Similarly, for PD, DisGeNET analysis identified that out of 20 genes, 17 genes were related to the terms- 'Parkinson's disease', 9 were associated with Lewy body disease and 10 were related to parkinsonian disorders. OMIM disease analysis screened 5 genes related to the term –'Parkinson's disease'.

3.4 DISCUSSION

We opted for a comprehensive data analysis approach to identify neuroprotective anticancer drugs and analyzed the data with network-based and pathway-based tools. We identified AD (49 genes) and PD-related (52 genes) by combining GWAS, transcriptomics, and metabolomics studies. We identified different PPI interactors of these genes and mapped them against approved anticancer drugs. For AD, 36 approved anticancer drugs and for PD 44 approved anticancer drugs were selected. Computational validation by CoDReS ranked the repurposing drugs based on their functional and structural properties. Among the proposed drugs, dasatinib (phase I/II), and bosutinib (Phase I) are in clinical trials as repurposed therapeutics for AD while nilotinib (phase II) is in clinical trials for

AD and PD, thus, validating the authenticity of our drug repurposing approach. The top scoring drugs obtained from CoDReS scoring were analyzed for their similarities with the known AD and PD drugs. We selected the closest neighbors- vandetanib, erlotinib, gefitinib, afatinib, imatinib, and sunitinib. The literature studies have confirmed the repurposing potential of these anticancer drugs. The ADMET analysis of these 6 drugs revealed that afatinib and imatinib did not possess good physicochemical properties and were not BBB penetrant. Thus, we proposed vandetanib, erlotinib, gefitinib, and sunitinib as potential repurposing drugs.

The pathway analysis identified EGFR as the most frequently appeared gene in AD and PD-associated pathways. Literature studies have supported the neuroprotective potential of EGFR and its associated drugs. In short, our integrated omics analysis with computational validation tools prioritized the role of EGFR in AD and PD pathogenesis. However, the therapeutic relevance of targeting EGFR in AD and PD is not well established. Still, some studies have supported the fact that EGFR prevents Aβ and ApoE-induced cognitive deficits and is considered a preferred target for treating AD [354],[332]. EGFR and its downstream targets are also known for promoting neurodegeneration and neuronal apoptosis in dopaminergic neurons in PD brains [355]. We also established a new connection of EGFR with AD and PD-related targets such as APP, SNCA, LRP1, and NRG (AD) and LRRK2, MAPT, SH3GL2 and UCHL1 (PD). Many bibliographic mentions also supported this finding. A recently published study has identified that APP-EGFR interaction promoted ERK signaling and contributed to neuritogenesis and neuronal differentiation [356]. Some studies have reported that EGFR has structural and expression similarities with ErBb4, the primary receptor of NRG1, in several brain regions. Some studies have found that EGFR was coexpressed with ErBb4 in several GABAergic neurons [357],[358]. This finding would help establish new connections of EGFR inhibitors with

NRG1. Although the role of EGFR in SNCA gene polymorphisms in AD brains is not explored but a study by Yan et al. confirmed that SNCA plays a significant role in EGFR signaling in lung adenocarcinoma cells [359]. In PD, LRRK2 is responsible for delaying EGFR trafficking and degradation in Rab7-dependent manner [360]. The relationship of SH3GL2 with EGFR is established in NSCLC where SH3GL2 gene is known to control tumor growth and progression by modulating EGFR function [361]. Although the association of UCHL1 with EGFR in PD is not recognized, a study has revealed that UCHL1 promotes EGFR downstream pathways by stabilizing EGFR levels [362]. Our proposed repurposed drug list had 3 EGFR inhibitors - vandetanib, erlotinib, and gefitinib. Among the proposed drugs, vandetanib, a tyrosine kinase inhibitor, is currently marketed to treat tumors of the thyroid gland. Likewise, erlotinib, an EGFR inhibitor, is used for treating non-small cell lung cancer (NSCLC) and pancreatic cancer. Similarly, gefitinib, an inhibitor of EGFR tyrosine kinase, is approved to treat locally advanced or metastatic non-small cell lung cancer. Structural similarities of these drugs with approved AD and PD drugs, physicochemical, and BBB analysis also supported the therapeutic potential of these drugs. Earlier studies have proposed that erlotinib and gefitinib rescued EGFR induced Aβ toxicity and memory loss in Drosophila and mouse models [332], but the exact molecular mechanism and affected signaling pathways are yet to be elucidated. By the same token, gefitinib is known for its neuroprotective functions in PD by inducing Parkin/PINK1 mediated mitophagy [334].

Further, some recent computational studies have predicted the potential drug-disease relations based on miRNA data. Based on this fact, we searched for miRNAs that were related to AD and PD and correlated the gene targets of those miRNAs with the gene targets of the proposed repurposed drugs. From this analysis, we identified some neuroprotective microRNAs and established their relationship with the repurposed drugs. We identified

miRNA-200a as a potential neuroprotective candidate for AD and miRNA-409 and miRNA-7-3 for PD that share targets with all three repurposed EGFR inhibitors. In such a way, miRNA-disease-drug relations helped us to establish a link between repurposed drugs and AD and PD concerning the miRNA axis.

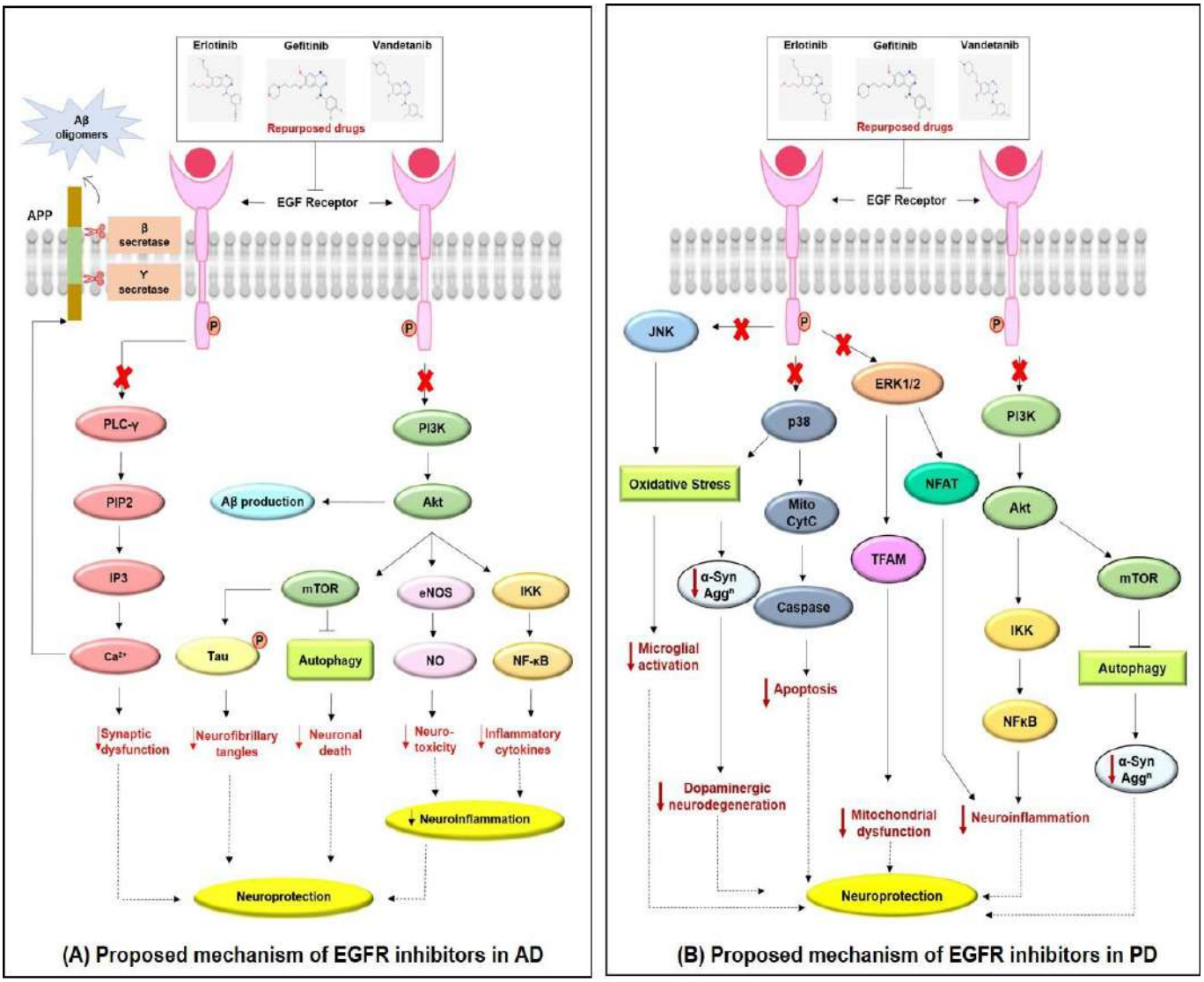


Figure 3.12: Schematic representation of the proposed mechanism of neuroprotective functions of EGFR inhibitors in (A) Alzheimer's and (B) Parkinson's Disease. The binding of a ligand to EGFR receptor causes conformational changes in the receptor and activates various signaling cascades. Activation of PI3K/Akt axis activates mTOR that is a major inhibitor of the autophagic process. The inhibition of autophagy leads to neuronal death. Activated mTOR is responsible for tau phosphorylation, Aβ production and alpha-synuclein aggregation, the major pathological hallmarks of AD and PD. Activated Akt further induces endothelial nitric oxide synthase (eNOS) that generates nitric oxide (NO), a neurotoxin. The activated Akt instigates inflammatory cytokine production by inducing NF-κB production. The activated EGFR receptor induces Ca^{2+} release from the endoplasmic reticulum by inducing Phospholipase C gamma (PLC-γ) production. Excessive release of Ca^{2+} causes synaptic dysfunction and Aβ production from amyloid precursor protein (APP). Activated EGFR also induce p38 kinase which activates apoptotic processes and dopaminergic neurodegeneration. All the events trigger neuroinflammation and neurodegeneration. Pharmacological inhibition of EGFR by inhibitors- erlotinib, gefitinib, and vandetanib, may

reverse the downstream signaling cascades of EGFR and provide neuroprotection a reduction in synaptic dysfunction, attenuation of protein aggregation, reduced tau phosphorylation, inhibition of neuronal death, and inhibition of neuroinflammatory processes. Dotted arrows represent the proposed neuroprotective functions of the repurposed drugs.

To determine the significance of the results, we curated the available literature and proposed the potential neuroprotective functions of the repurposing drugs in AD and PD pathogenesis, as shown in **Figure 3.12.** We suggested tau phosphorylation, autophagy, and neuroinflammation were the significant AD-related biological mechanisms regulated by the proposed EGFR inhibitor drugs. PI3-Akt signaling, NF-kappa B pathway, and Ca^{2+} signaling were the significant pathways targeted by the proposed drug. Likewise, for PD, the repurposed drugs are proposed to target α-syn aggregation, microgliosis, dopaminergic neurodegeneration, and mitochondrial dysfunction.

3.5 KEY HIGHLIGHTS OF THE STUDY

- ✓ EGFR as potential therapeutic target in AD and PD pathogenesis
- ✓ Vandetanib, Erlotinib, and Gefitinib as putative therapeutic agents in AD and PD pathology
- ✓ Vandetanib, Erlotinib, and Gefitinib alleviates AD and PD pathogenesis through EGFR signaling
- ✓ EGFR inhibitors reverses neuroinflammation, protein aggregation, neuronal apoptosis and provides neuroprotection in AD and PD
- ✓ AD- related miRNA-200a and PD-related miRNA-409 and miRNA-7-3 interact with proposed repurposed anticancer drugs vandetanib, erlotinib, and gefitinib

CHAPTER IV

DECIPHERING THE MOLECULAR MECHANISM AND CROSSTALK BETWEEN PARKINSON'S DISEASE AND BREAST CANCER THROUGH MULTI-OMICS AND DRUG REPURPOSING APPROACH

CHAPTER IV: DECIPHERING THE MOLECULAR MECHANISM AND CROSSTALK BETWEEN PARKINSON'S DISEASE AND BREAST CANCER THROUGH MULTI-OMICS AND DRUG REPURPOSING APPROACH

4.1 INTRODUCTION

PD is the second most prevailing neurodegenerative disorder characterized by progressive dopaminergic neuronal loss and intraneuronal alpha-synuclein aggregation. The complex neurodegenerative disorder is manifested by both motor and non-motor features that eventually appear during disease progression. According to the latest reports by the Michael J. Fox Foundation for Parkinson's Research (MJFF), the annual medical and economic burden to the US government and its individuals due to PD is $51.9 billion annually. To date, several treatment regimens targeting the dopaminergic approach are available for PD treatment. Still, none of them effectively halt disease progression and are also associated with several issues such as motor complications, altered BBB permeability and less life span [363]. Therefore, it is difficult to achieve big breakthroughs through traditional treatments, and novel disease-modifying options are being explored.

Recently, drug repurposing by computational methods has been emerged rapidly to discover new drug-disease relationships [364]. Starting the drug development process with an existing drug bypasses the tedious and costly preclinical stages, and success rates have been reported to reach 30% [365]. The drugs repurposed for PD focused on enhancing the potency of the standard drug L-Dopa, however, its use is associated with motor complications. The earliest successful repurposing example in PD is Amantadine, an anti-viral agent that has been repurposed for treating PD-related motor symptoms [366].

Epidemiological studies have reported an inverse association between PD and cancer, where many neoplasms are associated with lower cancer risk while some of them are found

to be at higher risk[367]. However, both the indications are multifactorial, and their causal relationship is not clear yet, especially in the case of breast cancer (BRCA). Earlier studies have reported an increased risk of breast cancer and higher mortality in women diagnosed with PD[368]. A meta-analysis study has reported a lack of correlation between PD and risk of breast cancer. In a Danish population-based cohort study, an increased risk of grade 1 breast tumors was found in PD patients [369]. A study published in the 2018 International Congress has claimed that females with breast cancer are at higher risk of developing PD when treated with chemotherapy drug tamoxifen[370]. Although the exact shared molecular mechanisms are unexplored, some studies have proposed that estrogen is neuroprotective and thus provides neuroprotection against PD [371]. Besides, mutations associated with many genes, including ATM (ataxia telangiectasia mutated), PARKIN and tumor suppressors the fact that increased levels of transcripts of the genes related to neurodegeneration, including Seladin-1, APP and PSEN1 are found in estrogen and progesterone receptor-negative (ER^-/PR^-) breast cancers [372].

The present study is the first to explore the molecular association between PD and BRCA. We aimed to identify the common gene signatures associated with PD and BRCA by integrating multiple omic studies. We also used different enrichment methods and protein-protein interaction analysis methods to find commonly dysregulated pathways and the possible crosstalk between PD and BRCA. The next step was to identify the repurposed drugs for PD by establishing a drug-drug relationship with the approved BRCA drugs. Our findings have increased the understanding of common dysregulation between PD and BRCA, and this may further provide a way to explore new therapeutic agents.

4.2. METHODOLOGY

4.2.1 IDENTIFICATION OF SHARED MOLECULAR SIGNATURES BETWEEN PD AND BRCA

To identify the common molecular signatures between PD and BRCA, we first extracted the total number of genes and variants associated with AD, PD and the thirteen most frequently appeared cancers (as identified by NCI) from DisGeNET database. Further, we compared AD, PD with different cancers concerning their common genes and variants.

4.2.2 DATA ACQUISITION FROM GWAS, TRANSCRIPTOMIC AND PROTEOMIC STUDIES

GWAS data for PD and BRCA was downloaded from the NHGRI-EBI catalog that contains information about SNP-trait associations [308]. For each SNP, information about associated allele, reported gene, p-value, associated trait, and study accession was collected. For the collection of transcriptome data, we browsed the GEO RNA-seq Experiments Interactive Navigator (GREIN) database, which is an interactive platform for analysis of GEO RNA-seq data[310]. GSE 136666 contains information of RNA sequencing data of 8 PD and 8 control patients from substantia nigra and putamen regions. GSE52194 includes the mRNA expression profiles of 17 breast tumor samples of three different subtypes and normal breast tissue. The information about proteins associated with PD and BRCA was extracted from the UniProt Knowledgebase (UniProtKB), a platform to access functional information on proteins [312]. For each UniProtKB entry, the protein name and associated gene names were identified.

4.2.3 DATA PROCESSING AND ANALYSIS

Data processing and management were performed to process raw data into standardized tables for every omics layer. SNP functional annotation was performed by the rSNPBase database to identify SNP-related regulatory elements and their associated target genes[373]. The raw transcriptomic data was processed to select genes with a false

discovery ratio (FDR) ≤ 0.05 and the fold change (lof2FC) = 2. The proteomic data with missing gene names were removed, and that contained multiple gene names were separated. The next step was finding the intersection of the three omics layers to test is there any significant association between the three omics layers for PD and BRCA. The intersection was performed using the online tool InteractiVenn, which provides an online interface to construct Venn diagrams for different biological datasets[374]

4.2.4 PPI NETWORK ANALYSIS

The PPI network was constructed by using an online tool, NetworkAnalyst, by putting all the common genes as seed proteins. NetworkAnalyst provides a comprehensive platform for network analysis and visualization by integrating information available in different databases [375]. The topological parameters such as degree centrality and betweenness distribution were calculated by a network analyzer in Cytoscape. Additionally, the module explorer panel was used to identify the connected proteins referred to as modules in the network. The different modules were given ranks based on the number of seed proteins involved.

4.2.5 IDENTIFICATION OF COMMON REGULATORY SIGNATURES

To identify the common regulatory elements at transcriptional and post-transcriptional levels, the overlapping genes were searched against different databases to find common transcription factors (TFs) and miRNAs for PD and BRCA. The TFs were identified against the JASPAR database, containing curated and non-redundant experimentally defined TF binding sites [376]. miRNAs were identified using the TarBase database, having experimentally validated miRNA targets of different species [377]. The TF-gene and miRNA-gene interaction networks were constructed and analyzed with NetworkAnalyst.

4.2.6 PATHWAY ANALYSIS

To understand the associated molecular functions, biological processes and signaling

mechanisms, the identified overlapping genes were subjected to GO term analyses and pathway analyses with the online available tool Enrichr. Enrichr is an online search engine with more than 300 gene set libraries of 400,000 annotated gene sets[378]. The <0.05 P-value cut-off was considered to select significant ontology terms. For pathway analysis, information related to three different databases-KEGG, Biocarta and Wiki pathways were retrieved.

4.2.7 IDENTIFICATION OF REPURPOSED DRUG CANDIDATES THROUGH LINCS L1000 AND CMAP ANALYSIS

We identified the drugs indicated for PD and BRCA from multiple sources, including Drugbank and the NCI drug repository. The transcriptomic effects produced by PD-related drugs were generated using LINCS 1000 data by identifying consensus signatures for each drug. The iLINCS (Integrative LINCS) portal allows transcriptional analyses of different drug signatures based on the Board L1000 assay. To determine the drug similarities with existing BRCA drugs, a comparative analysis was performed with the signatures of existing BRCA drugs. The similarities were calculated based on the concordance scores. The BRCA drugs having a positive correlation with the available PD drugs were further analyzed by the connectivity map (Cmap) that integrates more than 1 million profiles of chemical, genetic and disease perturbations in different cell types [379]. The list of PD-related gene signatures was generated by functional enrichment analysis of the PD-associated genes found from three different omics layers. The connection of query drugs to PD-related gene signatures was analyzed using the Touchstone tool. The correlation was calculated based on the CMap connectivity scores ranging from -100 to 100. Drugs showing a negative correlation with PD gene signatures were considered the potential repurposing candidates in reversing PD-related symptoms.

4.2.8 SCORING AND RANKING OF REPURPOSED DRUGS

The drugs obtained from the previous step were used as an input to CoDReS tool. The tool assigns a functional score (FS) and a structural score (StS) to each drug with respect to the disease of interest and gives a combined repurposing score (CoDReS) or a priori score (aS) [322].

The complete pipeline is shown in **Figure 4.1.**

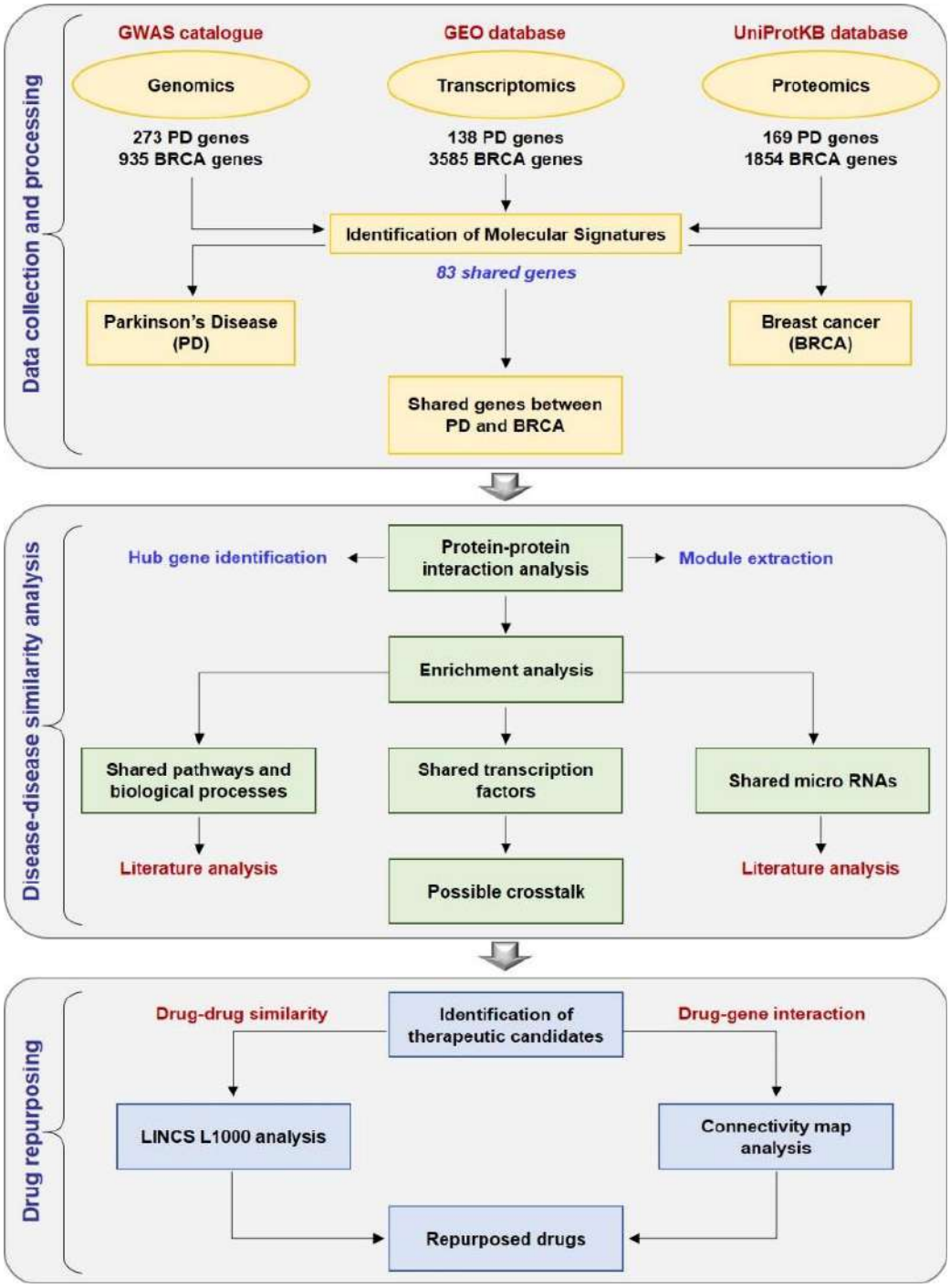


Figure 4.1: Workflow overview. Data collection was performed from Genome-wide association studies catalog (GWAS) for genomic studies, Gene expression omnibus (GEO) database for transcriptomics studies and UniProtKB database for proteomics studies. After data processing, the intersection of Parkinson's disease (PD) and Breast cancer (BRCA) per omics layer was done using Venn diagrams. Protein-protein interaction (PPI) analysis extracted common hub genes to search for disease-disease similarity. These hub genes were further subjected to enrichment analysis and pathway analysis to obtain significant pathways and common GO terms. The common regulation of the two indications was further confirmed by identifying common transcription factors (TFs) and microRNAs (miRNA). LINCS L1000 and connectivity map (Cmap) analysis was performed to identify potential repurposing drugs for PD. The drug-drug and drug-gene similarity analysis has given potential repuposed drugs.

4.3 RESULTS

4.3.1 IDENTIFICATION OF BRCA AS THE MOST COMMONLY ASSOCIATED CANCER WITH AD AND PD

From the DisGeNET database analysis, we identified that BRCA, colorectal cancer and melanoma were the top three cancers sharing signatures with both AD and PD, with BRCA ranked as the top cancer. The number of shared genes between BRCA and AD were 2182 while with PD were 1353. Likewise, the number of shared variants with AD and BRCA were 82 while between PD and BRCA were 80 **(Figure 4.2).**

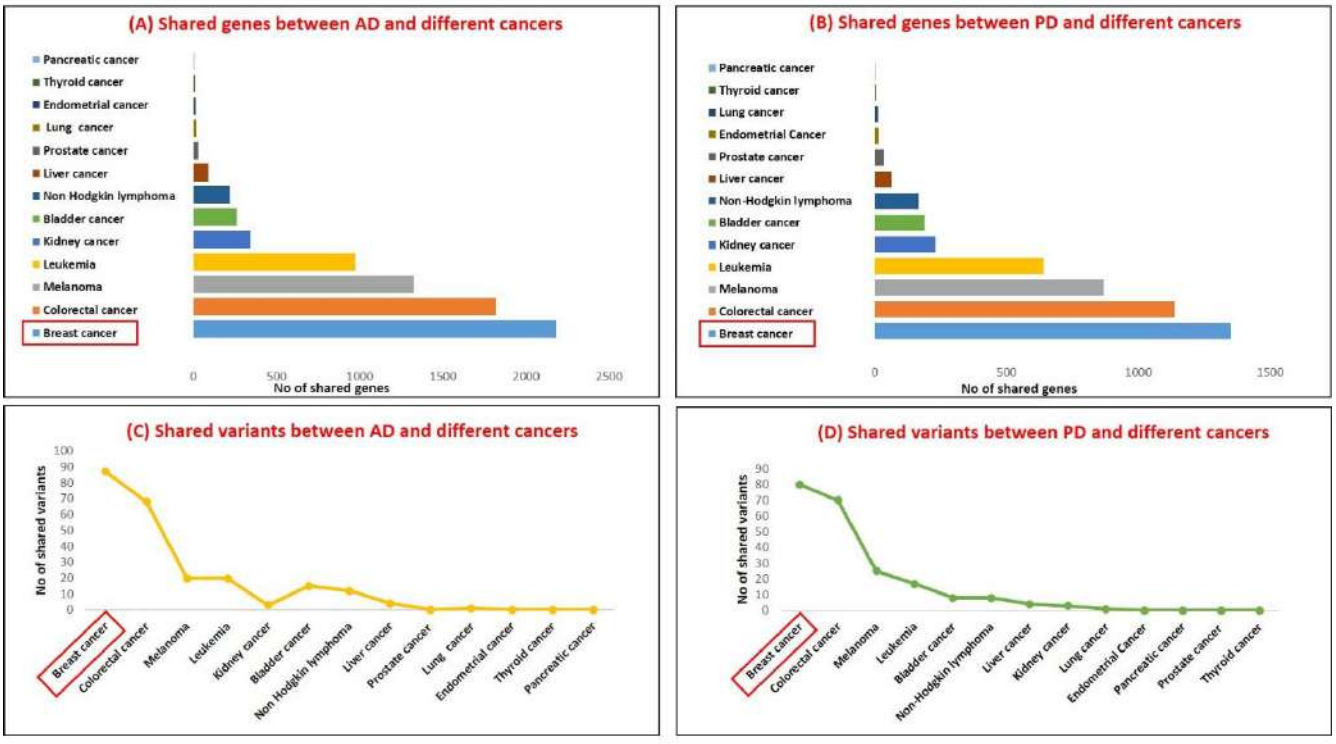


Figure 4.2: Comparison of number of shared genes and shared variants between AD, PD and thirteen different frequently appeared cancers. The data was collected from DisGeNET database.

4.3.2 OMICS ANALYSIS LINKS PD SIGNATURES WITH BRCA SIGNATURES

From 54 GWAS studies for PD, we identified 390 SNPs, while for 101 GWAS studies for BRCA, we found 1455 SNPs, out of which 211 SNPs were found functionally annotated with PD and 742 SNPs with BRCA. The PD-related SNPs were functionally annotated with 273 target genes, while BRCA related SNPs were associated with 935 different genes. For transcriptomic data, out of the 138 significant PD-associated genes, 50 genes were upregulated, and 88 genes were downregulated, while out of 3585 significant BRCA associated genes, 2695 were upregulated, and 890 genes were downregulated. The greatest fold differential expression for PD was observed 2.08-fold upregulation of RPS3AP3 gene and 2.05-fold downregulation of TPH2 gene. In the case of BRCA, the greatest 16.84-fold upregulation was for the RNVU1-7 gene and downregulation of 10.722- fold for the IL-6 gene. Similarly, we found 188 and 2628 proteins for PD and BRCA from the UniProtKB database that was related to 169 and 1854 genes, respectively.

To establish the common linkage between PD and BRCA at the molecular level, we identified different intersections between the two diseases per omics layer. For genomics, we identified 28 shared genes, for transcriptomics 40 genes and for proteomics 29 genes, as shown in the Venn diagrams **(Figure 4.3 A-C).** To identify the total number of shared genes between PD and BRCA, we combined the shared genes per omics layer resulted in 96 shared genes, out of which 13 belonged to non-coding proteins and were thus excluded from the study. The complete list of common genes is provided in **Annexure 5**. The expressed proteins of the 83 shared genes were analyzed for the functional categories **(Figure 4.3 D).** We found different categories- others (24%), mitochondrial enzymes (19%), other enzymes (12%), transcription factor (10%), immune function-related proteins (8%), structural protein (6%), regulatory proteins (7%), neuronal protein (4%), transporters

(4%), receptors (4%), and growth factor (2%). We found most of the proteins were related to mitochondrial processes and electron transport chain.

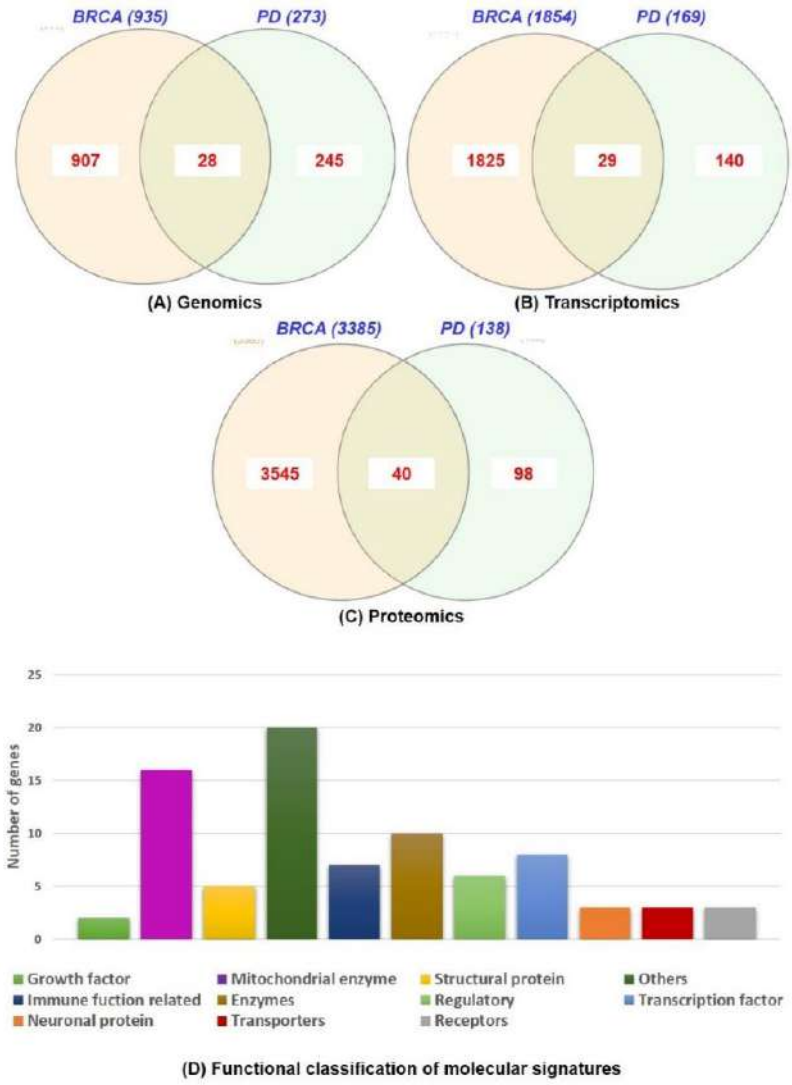


Figure 4.3: (A-C) Venn diagrams showing the overlap between genes obtained from genomic studies (A), transcriptomics studies (B), and proteomics studies (C) for breast cancer (BRCA) and Parkinson's Disease (PD). Significant overlaps have shown a significant number of shared genes for different omics layers. (D) The proteins encoded by the significant genes belong to different functional categories. We found mitochondrial enzymes, other enzymes and transcription factors as the top three significant functional categories. The number of genes are shown on the Y-axis.

4.3.3 PPI NETWORK ANALYSIS IDENTIFIES DYSREGULATED GENES LINKING PD AND BRCA

The shared interactants of Venn analysis of different omics data were combined to identify common gene signatures between PD and BRCA. We reported 83common genes, which

were then mapped in the form of PPI network. The PPI network was constructed to predict the significant biological interactions that play a key role in linking PD and BRCA. The resultant PPI network had 10 different subnetworks comprising a different number of nodes and interconnecting edges. We selected the largest subnetwork with 434 nodes and 472 edges for further analysis. To minimize the 'hairball effect', we constructed PPI network of first-order having seed nodes and other connecting nodes (**Figure 4.4A).** The PPI network was further assessed for different topological parameters, including degree centrality and betweenness. We observed degree with a range of 1 to 54 and betweenness with a range of 0 to 51830.58. We found that out of 434 nodes, 18 nodes had degree centrality value of ≥10. The nodes with higher values of degree were considered as hub nodes, while those with higher betweenness value were considered as bottleneck nodes. We found CAV1 (degree-54; betweenness-38225.17), PSMA8 (degree-47; betweenness-27751.2), EIF4G1 (degree-47; betweenness-17641.86), SQSTM1 (degree-36; betweenness-17059.53), and NSF (degree-29; betweenness-8703.19) as the top 5 hub nodes with highest values of degree in the network. These hub genes can be considered as the possible therapeutic targets as they are involved with shared signaling pathways. The description of all the hub proteins with topological parameters is provided in **Table 4.1.**

Table 4.1: Description of hub proteins with topological parameters

Protein	Description	Degree	Betweenness
CAV1	Caveolin-1	54	38225.17
PSMA8	Proteasome 20S subunit alpha 8	47	27751.2
EIF4G1	Eukaryotic translation initiation factor 4 gamma 1	47	17641.86
SQSTM1	Sequestosome-1	36	17059.53
NSF	N-Ethylmaleimide sensitive factor, vesicle fusing ATPase	29	8703.19
WNT3	Wnt family member 3	26	13016.88
UBTF	Upstream binding factor 3	26	10516.1
EFNA1	Ephrin A1	22	8355.92
BMP7	Bone morphogenetic protein 7	18	9829.46
NEK2	NIMA Related Kinase 2	18	6896.85
EGR2	Early growth response 2	16	5822.35
HSPA1B	Heat Shock Protein Family A (Hsp70) Member 1B	15	5957
UBC	Ubiquitin C	13	51830.58
MDC1	Mediator of DNA damage checkpoint 1	12	4697
SREBF1	Sterol Regulatory Element Binding Transcription Factor 1	11	9330.41
NOS2	Nitric oxidase synthase 2	11	6741.53
RNF11	Ring finger protein 11	11	3952.14
FOSB	Fos proto-oncogene, AP-1 transcription factor subunit	10	2623.37

***Highlighted rows represent the top 5 hub proteins**

The PPI network was further evaluated for module analysis to extract different modules having similar biological functions. We observed 22 different modules with p-value ≥ 0.05 and ranged in size from 5 to 61 genes. We selected the top 4 modules having different hub nodes interacting with different genes **(Figure 4.4 B-E).** Module 0 (p-value 5.94E-17) consisted of CAV1, NOS2 and KLK6 as hub nodes, module 1 (p-value 8.76E-09) had TBX2 and BMP7 hub nodes, module 2 (p-value 2.24E-05) had DUSP2 and FOSB hub nodes, and module 4 (p-value 0.00424) had SREBF1 and WWOX hub nodes.

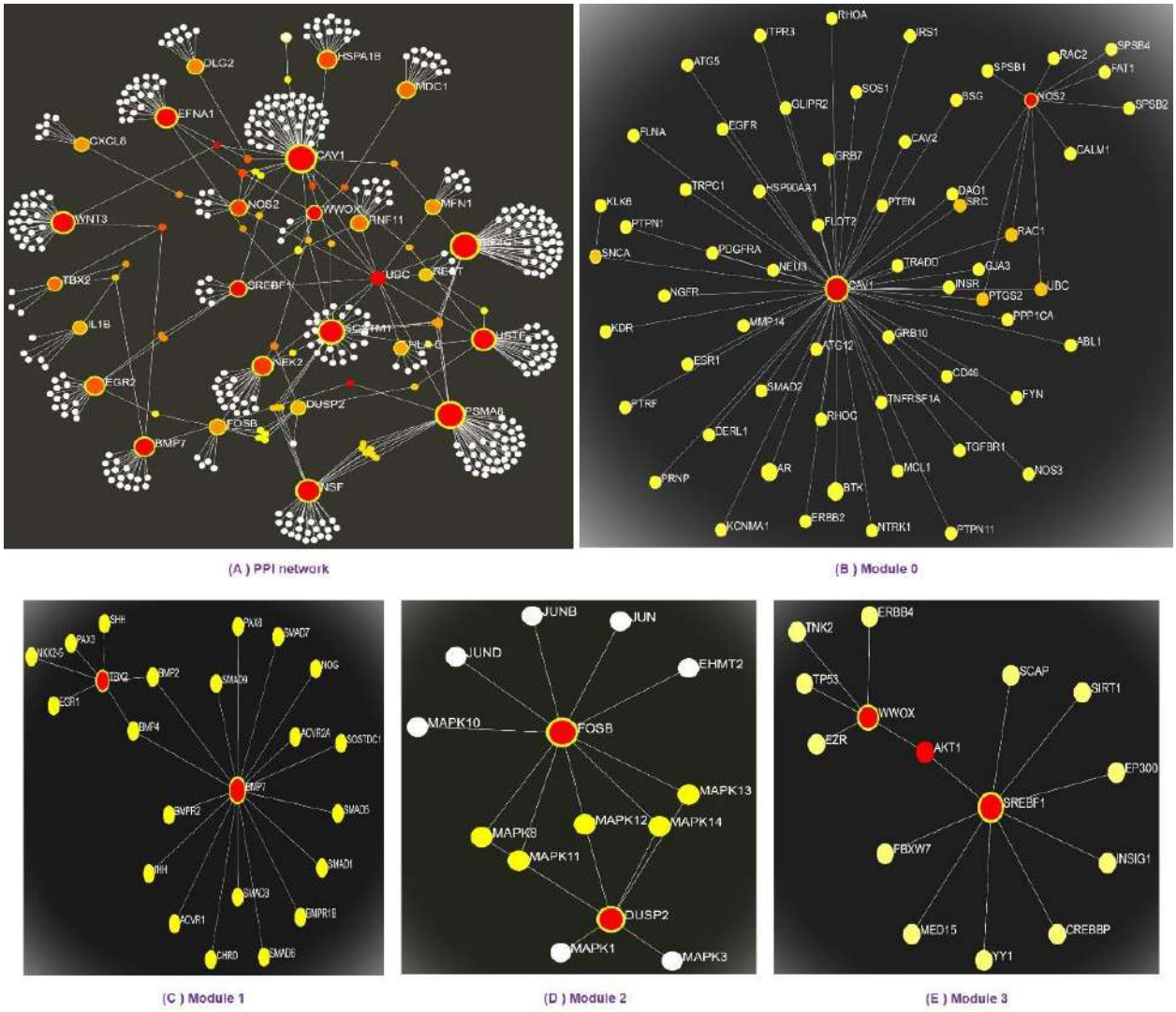


Figure 4.4: (A) Protein-protein interaction (PPI) network showing the hub genes where nodes represent the proteins and edges represent the connection. The query protein nodes are highlighted in yellow. The size of different nodes corresponds to their degree centrality values in the network. Different significant modules have been extracted from the PPI network, and the top four modules were selected for further analysis. (B) Module 0 has three query nodes CAV1, NOS2 and KLK6. (C-E) Module 1 to module 3 have two query nodes each- module 1 has BMP7 and TBX2, module 2 has DUSP2 and FOSB and module 3 has WWOX and SREBF1.

4.3.4 IDENTIFICATION OF REGULATORY MOLECULES ESTABLISHES A COMMON LINK BETWEEN PD AND BRCA

To decode the disease-disease association at transcriptional and post-transcriptional levels, we found the connection of the hub genes with TFs and miRNAs, as shown in **Figure 4.5 A-B.** GATA2, NFIC, NFKB1, USF2, FOS, HOXA5, TP53, CEBPB, ELK1, and SRF were

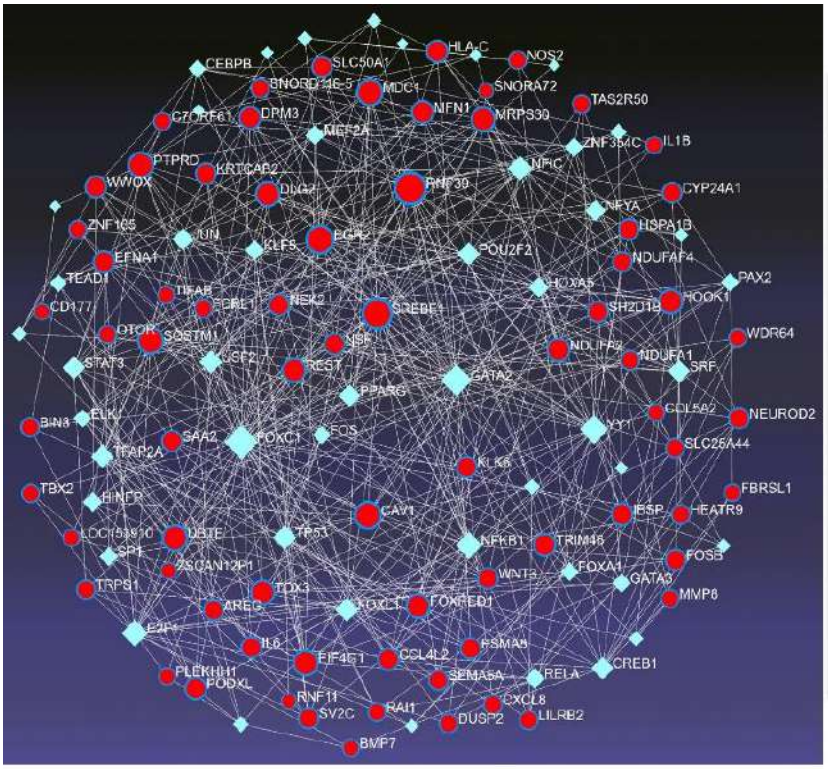
selected as the top interacting TFs with the hub genes. All the TFs play different roles in the pathogenesis of PD and BRCA **(Table 4.2).**

Table 4.2: Summary of top transcription factors and miRNAs associated with hub genes with their significance in PD and BRCA pathogenesis

Common transcription factors			
Factor	**Associated hub genes**	**Significance in PD**	**Significance in BRCA**
GATA2	ZSCAN12P1, NDUFAF4, MFN1, BIN3, SQSTM1, PTPRD, BIN3, CCL4L2, WWOX, UBTF, SAA2, EIF4AG1	Transcriptional regulation of SNCA gene expression	Associated with breast cancer progression by epigenetic regulation of G9a [380]
NFIC	HSPA1B, NEK2, UBTF, NDUFA2, CYP24A1, MRPS30, FOXRED1, DLG2	Serves as a regulatory transcriptional signature in PD [381]	Regulation of breast cancer progression via NFI-C-KLF4-E-cadherin pathway [382]
NFKB1	IL6, PODXL, SAA2, SQSTM1, NDUFA2, CCL4L2, EIG4G1, FOXRED1	Production of inflammatory mediators responsible for neurotoxicity [383]	Promotes tumor development, progression and chemoresistance in hormone-independent forms of breast cancer [384]
USF2	CCL4L2, WWOX, EIF4G1, PTPRD, SQSTM1, PODXL, MFN1	NA	Highly expressed in breast cancer and assists tumor progression [385]
FOS	IL6, IBSP, SQSTM1, PTPRD, SAA2, WWOX	Regulation of L-Dopa–induced dyskinesia (LID) [386]	Regulation of tumor invasion and metastasis [387]
HOXA5	BIN3, NDUFA2, FOXRED1, DLG2, NEK2, IBSP	NA	Overexpression is associated with the p53-dependent apoptotic pathway [388]
TP53	NDUFA2, FOXRED1, PTPRD, EIF4G1, UBTF	Functions as an anti-autophagic TF. Transcriptional repression of PINK1 [389]	Frequently mutated in BRCA, especially in triple-negative breast cancer [390]
CEBPB	WWOX, PTPRD, SQSTM1, MRPS30	Regulation of cleavage of α-synuclein and monoamine oxidase B activity [391]	Regulation of breast cancer cell invasion and migration through PAK4-CEBPB-CLDN4 axis [392]
ELK1	NEK2, BIN3, MFN1, UBTF	Cytoplasmic phosphorylation of the protein is associated with protein inclusions in PD [393]	Promotes breast cancer cell proliferation [394]
SRF	DLG2, NDUFA2, CYP24A1, SQSTM1	Important regulator of anti-apoptotic response in dopaminergic neurons [395]	Induction of mammary stem cell-like properties in BRCA [396]
Common miRNAs			
hsa-mir-335-5p	IL6, EFNA1, HSPAIB, CXCL8, REST, SQSTM1, NEUROD2, WNT3, HOOK1, SREBF1, AREG	Regulation of inflammation by targeting LRRK2 [397]	Regulation of BRCA1 gene expression [398]
hsa-mir-124-3p	CXCL8, TBX2, PODXL, EGR2, EFNA1, TRPS1, IL6, REST, DUSP2, CAV1, HSPAIB	Associated with neuroprotective properties by regulation of the ERK pathway [399]	Contributes to breast cancer tumorigenesis and targets Cbl prot-oncogene [400]
hsa-mir-26b-5p	MMP8, CYP24A1, NSF, PODXL, CAV1, TRPS1, RNF11, NDUFA1, SLC25A44	NA	Functions as a radiation biomarker in BRCA [401]

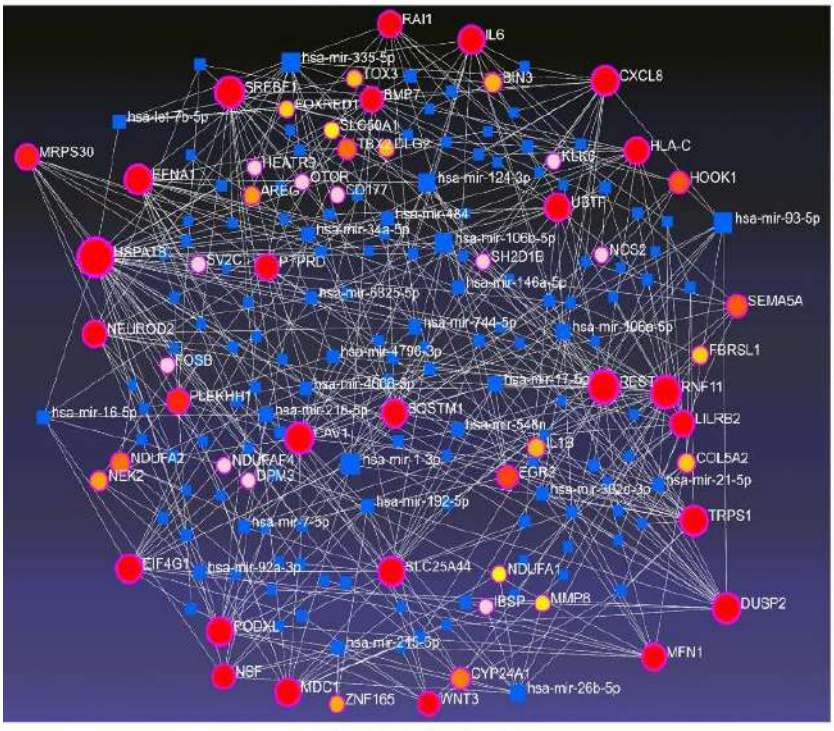
hsa-mir-1-3p	UBTF, BMP7, IL6, CXCL8, EIF4G1, TRPS1, MDC1, PTPRD, HOOK1	NA	Mediates breast cancer invasion and metastasis [402]
hsa-mir-93-5p	SLC25A44, DUSP2, REST, HOOK1, CXCL8, EGR2, MFN1, CAV1, SQSTM1	NA	Controls epithelial-mesenchymal-transition in breast cancer cells [403]
hsa-mir-106a-5p	DUSP2, REST, ILIB, IL6, CXCL8, MFN1, CAV1, SLC25A44	Associated with cognitive improvement in PD brains[404]	Serves an important biomarker for breast cancer progression[405]
hsa-mir-218-5p	TRPS1, SEMA5A, EFNA1, EIF4G1, PODXL, NSF, CYP24A1	Has neuroprotective effects on dopaminergic neurons [406]	Activation of Wnt signaling and regulation of breast cancer metastasis [407]
hsa-mir-106b-5p	DUSP2, HSPA1B, REST, SQSTM1, MFN1, CAV1, SLC25A44	NA	Regulation of breast cancer progression by suppression of PI3K/Akt pathway[408]
hsa-mir-17-5p	SCL25A44, SQSTM1, DUSP2, REST, EGR2, MFN1, CAV1	Associated with PD [409]	Acts as both tumor promoter and tumor suppressor[410]
hsa-mir-484	RNF11, HSPA1B, UBTF, HLA-C, SQSTM1, SREBF1	NA	Changes cytidine deaminase activity associated with breast cancer proliferation and chemoresistance [411]

Similarly, hsa-mir-93-5p, hsa-mir-1-3p, hsa-mir-106a-5p, hsa-mir-17-5p, hsa-mir-218-5p, hsa-mir-106b-5p, hsa-mir-149-3p, hsa-mir-16-5p, hsa-mir-192-5p, hsa-mir-34a-mir, hsa-mir-215-5p, hsa-mir-484, hsa-mir-744-5p were identified as the top interacting miRNAs with the hub genes. The relevance of these miRNAs in both PD and BRCA was identified and shown in (**Table 4.2).**



(A) TF-gene interaction network

TF	Degree
FOXC1	43
GATA2	33
YY1	27
E2F1	22
NFKB1	22
NFIC	19
FOXL1	16
TP53	16
POU2F2	15
SRF	15



(B) miRNA-gene interaction network

miRNA	Degree
hsa-mir-335-5p	15
hsa-mir-124-3p	12
hsa-mir-26b-5p	10
hsa-mir-1-3p	9
hsa-mir-93-5p	9
hsa-mir-106a-5p	8
hsa-mir-218-5p	7
hsa-mir-106b-5p	7
hsa-mir-17-5p	7
hsa-mir-484	6

Figure 4.5: (A) Transcription factor-hub gene network shows the interaction between the hub genes and associated transcription factors (TFs). The red circles represent the hub genes and the blue diamonds represent the associated TFs. (B) miRNA-gene interaction network links the hub genes through miRNAs. The red circles represent the hub genes and the blue squares represent the miRNAs. The associated tables show the top interacting TFs and miRNAs with their degree centrality values.

4.3.5 PATHWAY ANALYSIS IDENTIFIES OVERLAPPING OVER-REPRESENTED PATHWAYS AND GENE ONTOLOGIES ASSOCIATED WITH PD AND BRCA

To sketch the common pathway dysregulation between PD and BRCA, we performed pathway enrichment and gene ontology analysis of the hub genes. We reported 10 enriched KEGG pathways Prion disease (P-value 2.14E-18), oxidative phosphorylation (P-value 8.12E-17), pathways of neurodegeneration (P-value 5.97E-16), Alzheimer's disease (P-value 7.54-16), Parkinson's disease (P-value 3.11E-15), thermogenesis (P-value 1.86E-14), Diabetic cardiomyopathy (P-value 4.72E-14), Huntington disease (P-value 9.28E-14), and Amyotrophic lateral sclerosis (P-value 1.19E-13) having more than 10 overlapping genes in both disorders. From Bioplanet database, oxidative phosphorylation (P-value 1.14E-16), Parkinson's disease (P-value 6.43E-17), and electron transport chain (P-value 2.07E-18) were found enriched. From Wiki pathways, we found the electron transport chain (P-value 1.53E-18), mitochondrial complex I assembly (P-value 1.19E-13), and non-alcoholic fatty liver disease (P-value 3.72E-09) as enriched pathways. These results revealed that pathways enriched with the maximum number of shared genes were associated with electron transport chain and oxidative phosphorylation.

Table 4.3: Top 10 ontology terms associated with hub genes in PD and BRCA

Term	P-value	Genes involved
Biological process		
Regulation of cell adhesion molecule production (GO:0060353)	8.82E-06	CXCL8;CAV1;IL1B
Positive regulation of neuroinflammatory response (GO:0150078)	2.28E-05	IL6;IL1B;MMP8
Positive regulation of interleukin-6 production (GO:0032755)	3.24E-05	IL6;NOS2;IL1B;LILRB2;MMP8
Negative regulation of nervous system development (GO:0051961)	9.82E-05	IL6;REST;IL1B
Regulation of neuroinflammatory response (GO:0150077)	9.82E-05	IL6;IL1B;MMP8
Mitochondrial respiratory chain complex I assembly (GO:0032981)	1.73E-04	NDUFAF4;NDUFA2;NDUFA1;FOXRED1

NADH dehydrogenase complex assembly (GO:0010257)	1.73E-04	NDUFAF4;NDUFA2;NDUFA1;FOXRED1
Regulation of interleukin-6 production (GO:0032675)	1.89E-04	IL6;NOS2;IL1B;LILRB2;MMP8
Positive regulation of interleukin-8 production (GO:0032757)	2.11E-04	IL6;NOS2;IL1B;HSPA1B
Regulation of neurogenesis (GO:0050767)	2.25E-04	IL6;REST;IL1B;WNT3
Cellular function		
Mitochondrial respiratory chain complex I (GO:0005747)	0.001074	NDUFA2;NDUFA1;FOXRED1
Respiratory chain complex I (GO:0045271)	0.001074	NDUFA2;NDUFA1;FOXRED1
Mitochondrial inner membrane (GO:0005743)	0.00501	CYP24A1;NDUFAF4;NDUFA2;NDUFA1;MRPS30;FOXRED1
Organelle inner membrane (GO:0019866)	0.006462	CYP24A1;NDUFAF4;NDUFA2;NDUFA1;MRPS30;FOXRED1
Endocytic vesicle membrane (GO:0030666)	0.007097	CAV1;HLA-C;AREG;WNT3
Mitochondrial membrane (GO:0031966)	0.007412	CYP24A1;NDUFAF4;NDUFA2;MFN1;NDUFA1;MRPS30; FOXRED1
Aggresome (GO:0016235)	0.012239	SQSTM1;HSPA1B
Anchored component of plasma membrane (GO:0046658)	0.020577	EFNA1;CD177
Mitochondrial envelope (GO:0005740)	0.023292	NDUFAF4;NDUFA2;NDUFA1
Filtration diaphragm (GO:0036056)	0.023773	PODXL
Molecular function		
Cytokine activity (GO:0005125)	1.87E-04	IL6;CXCL8;CCL3L1;IL1B;BMP7;WNT3
Ionotropic glutamate receptor binding (GO:0035255)	0.001001	NSF;SQSTM1
Glutamate receptor binding (GO:0035254)	0.002959	NSF;SQSTM1
Receptor ligand activity (GO:0048018)	0.003637	SEMA5A;IL6;IL1B;AREG;BMP7;WNT3
NADH dehydrogenase (quinone) activity (GO:0050136)	0.012239	NDUFA2;NDUFA1
NADH dehydrogenase (ubiquinone) activity (GO:0008137)	0.012239	NDUFA2;NDUFA1
Growth factor receptor binding (GO:0070851)	0.014119	IL6;IL1B;AREG
Chemokine activity (GO:0008009)	0.020577	CXCL8;CCL3L1
Syndecan binding (GO:0045545)	0.023773	SEMA5A
Chemokine receptor binding (GO:0042379)	0.024056	CXCL8;CCL3L1

The comparative analysis of different enriched pathways from different databases is shown in **Figure 4.6A-C**. Similarly, we identified the significant GO terms (biological processes, cellular function and molecular function) shared between PD and BRCA. We found regulation of interleukin-6 production (GO:0032755;5 genes), mitochondrial respiratory chain complex I assembly (GO:0032981; 4 genes), NADH dehydrogenase complex assembly (GO:0010257;4 genes), positive regulation of interleukin-8 production (GO:0032757;4 genes) and regulation of neurogenesis (GO:0050767;4 genes) as the top 5

biological processes comprised of the maximum number of common genes. The complete list of top ontology terms identified is shown in **Table 4.3.**

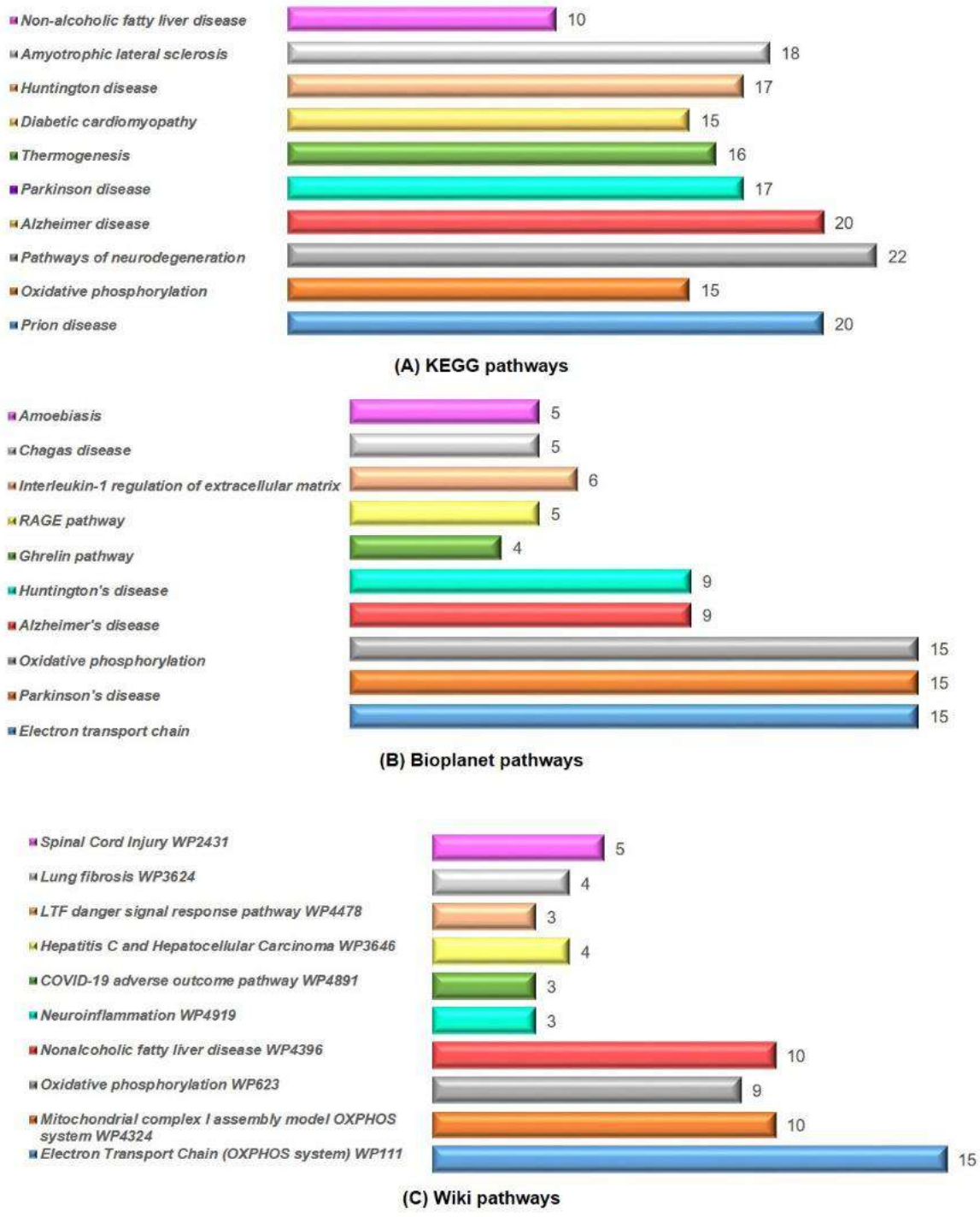


Figure 4.6: Graphical representation of the enriched pathways of shared genes between PD and BRCA. (A) KEGG pathways, (B) Bioplanet pathways and (C) Wiki pathways. Each color represents a different pathway and the numbers represent the total number of genes associated with a specific pathway. For KEGG pathways, pathways of neurodegeneration (22 genes), Alzheimer's Disease (20 genes), and Prion disease (20 genes) are the most enriched pathways. For Bioplant pathways, oxidative phosphorylation,

Parkinson's disease and electron transport chain, each with 15 genes, are the top three significant pathways. Similarly, for Wiki pathways, electron transport chain (15 genes), non-alcoholic fatty liver disease (10 genes), and mitochondrial complex I assembly (10 genes) are the significant pathways.

4.3.6 LINCS L1000 AND CMAP ANALYSIS IDENTIFIES POTENTIAL REPURPOSING DRUG CANDIDATES BASED ON GENE EXPRESSION SIGNATURES

To investigate the potential role of BRCA drugs in PD treatment, we explored the gene expression signatures generated by the drugs for the two indications. First, we obtained the drug list for PD from Drugs.com. The information on BRCA drugs was retrieved from the National Cancer Institute's (NCI) comprehensive database that contains information of the FDA-approved and investigational cancer drugs and combinations. We collected 38 approved breast cancer drugs by omitting information of any investigational drugs and drug combinations (**Annexure 7**). Further, the consensus signatures for each PD drug were obtained from the LINCS L1000 database and compared with consensus signatures of BRCA drugs. The BRCA drugs with a positive correlation with PD drugs were considered for further analysis. We found positive correlations of BRCA drugs with seven PD drugs. The observed correlations were plotted in a heat map where the red color represents positive correlation and the blue color represents no correlation **(Figure 4.7A).** For instance, tolcapone, a catechol-O-methyl transferase (COMT) inhibitor was correlated with a maximum of eleven BRCA drugs- alpelisib, anastrozole, doxorubicin, Fluorouracil, lapatinib, mitoxantrone, olaparib, palbociclib, raloxifene, thiotepa and toremifene. Similarly, rasagiline, an irreversible monoamine oxidase B (MAOB) inhibitor was related with six BRCA drugs-alpelisib, everolimus, lapatinib, mitoxantrone, neratinib, and palbociclib. The dopamine precursor levodopa used for PD treatment was correlated with five BRCA drugs- lapatinib, mitoxantrone, olaparib, palbociclib, and tamoxifen. Selegiline, another MAOB inhibitor was related to four BRCA drugs- cyclophosphamide, lapatinib, mitoxantrone, and neratinib. For carbidopa, a dopa decarboxylase inhibitor, we

found two BRCA drugs- lapatinib and neratinib; for pramipexole, a dopamine agonist, only one drug- raloxifene and for benztropine, an anticholinergic, only one drug- cyclophosphamide.

To further support our drug repurposing strategy, we explored the connections of BRCA drugs with PD gene signatures (**Annexure 6**). We observed that only a few BRCA drugs were correlated with PD gene signatures. We considered negative correlations that mean the drug can reverse the effects of the associated gene signatures and is thus considered a potential repurposing drug. We found 11 BRCA drugs with good connectivity scores with PD gene signatures. The observed drug-gene correlations were shown in a heat map where the red color represents positive correlations, and the blue color represents negative correlations **(Figure 4.7B).**

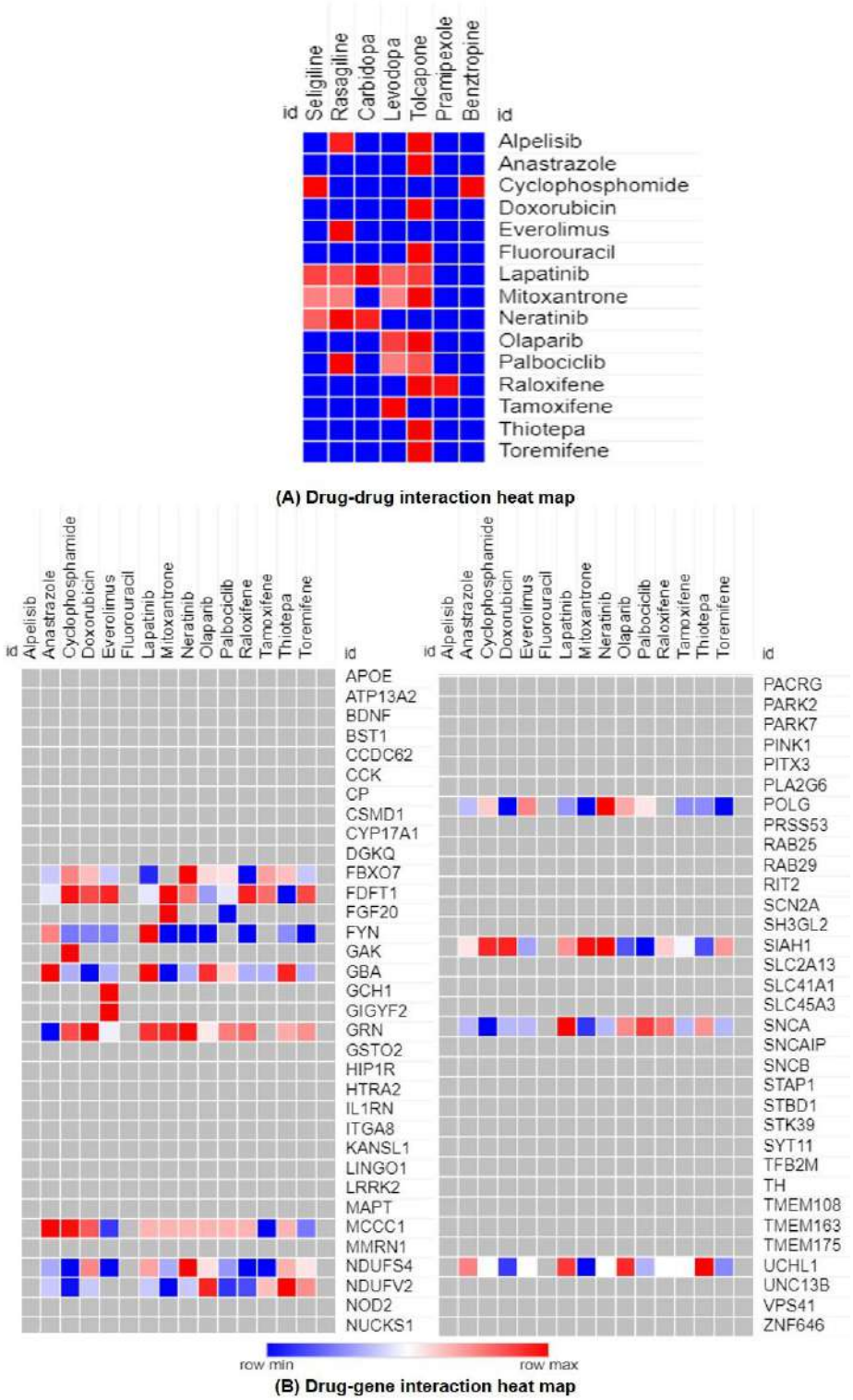


Figure 4.7: (A) LINCS L1000 derived top breast cancer-related drugs mimicking the gene expression profiles of Parkinson's disease-related drugs. Red color represents correlation, and blue color represents no correlation. (B) Connectivity map analysis of breast cancer drugs with PD-related gene expression signatures. Red color represents positive correlation, and blue color represents negative correlation. Alpelisib and Fluorouracil have shown no interaction with PD-related gene expression signatures.

4.3.7 CODRES RE-RANKING PRIORITIZED POTENTIAL REPURPOSING DRUGS FOR PARKINSON'S DISEASE

The repurposed drugs from CMap and LINCS L1000 analysis were analyzed for the structural and functional properties. The comparative structural, functional and composite scores were represented in **Figure 4.8**. The values have indicated that most of the drugs have similar structural scores but functional scores have great variations. We found that four drugs- palbociclib, cyclophosphamide, olaparib and thiotepa have structural score value 1 and only one drug tamoxifen has functional score value 1. It was observed that anastrazole was assigned with 0 value in terms of both structural and functional scores. The drugs were ranked based on their composite CoDReS scores and tamoxifen, raloxifene, palbociclib, cyclophosphamide, and olaparib were the top 5 drugs. We considered the selective estrogen receptor modulators- tamoxifen and raloxifen with the highest CoDReS scores as the most promising repurposed drugs for PD.

Figure 4.8: Computational drug repurposing score (CoDReS) analysis of drugs. The structural scores of the drugs are more or less similar while the functional scores have shown variations. The drugs were given ranks based on their combined scores. The combined scores range from 0 to 1. Anastrazole has functional, structural and combined scores of 0. Tamoxifen and raloxifene had the highest functional, structural and combined scores.

4.4 DISCUSSION

To the best of our knowledge, the present study is the first to dissect the common molecular mechanism between PD and BRCA at the multi-omics level and to identify the repurposed drugs for PD from the available pool of BRCA drugs BRCA. We combined the data from three different omics layers (genomics, transcriptomics and proteomics) and analyzed the associated pathways, biological processes and therapeutic molecules. From the integrated analysis, we identified the total number of overlapping genes between PD and BRCA. We found 28 overlapping genes from genomics, 40 genes from transcriptomics and 29 genes from proteomics studies. We found that the total number of overlapping genes on genomics and proteomics layers were relatively low than in the transcriptomics layer.

We identified different hub genes based on topological parameters. These hub genes are assumed to play a crucial role in disease pathogenesis and are associated with several biological processes in PD and BRCA, as reported in the literature. Different enrichment analysis methods have been used to establish a connection of dysregulated pathways between PD and BRCA. We identified electron transport chain (ETC), oxidative phosphorylation and pathways of neurodegeneration as the most commonly dysregulated pathways from KEGG, Bioplanet and Wiki pathway analysis. Downstream analysis has identified ND1, ND2, ND3, ND4, ND5, ND6, NDUFA1, NDUFA2, COX1, COX2, COX3, CYTB, ATP6, and ATP8 were the most frequently appeared genes in the identified dysregulated pathways. Numerous studies have highlighted the role of defective ETC components in PD pathogenesis. The defects in mitochondrial complex I are associated with neuronal apoptosis and are involved in reactive oxygen species (ROS) generation [412]. Aberrations in mitochondrial complex I activity is known to induce breast tumor aggressiveness, and therapeutic enhancement of the activity inhibits disease progression. The altered activity of oxidative phosphorylation (OXPHOS) components and mutations

in mtDNA and nuclear genes encoding OXPHOS subunits have been associated with PD pathogenesis [413]. Studies have indicated that OXPHOS is upregulated in BRCA cells and OXPHOS inhibitors can be used as therapeutic agents in BRCA [414]. A recent study based on genetic and transcriptomic data has also revealed that mitochondria-related processes such as OXPHOS and ATP synthesis are frequently enriched pathways for genes related to AD, PD, and cancer [415].

To further establish the connection between PD and BRCA, we identified the regulatory signatures (TFs and miRNAs) associated with both pathologies. Among the top interacting TFs, GATA2 (GATA-binding factor 2) is reported to be highly expressed in substania nigra and regulates the expression of SNCA gene in human dopaminergic cells. Similarly, GATA2 has been documented as a tumor suppressor gene in hypoxia-mediated BRCA cell survival and tumorigenesis. In a study, nuclear factor I-C (NFI-C) is reported to be a crucial transcriptional signature in PD [381]. In the same way, this TF is known to be involved in the NFI-C-KLF4-E-cadherin pathway to assist breast cancer tumorigenesis [382]. Another TF, NF-κB (Nuclear factor κB), a proinflammatory TF, is known to be associated with dopaminergic neurotoxicity by inducing the production of inflammatory mediators [383]. The role of NF-*K*B in BRCA pathogenesis is well established as the TF facilitates the development and progression of hormone-independent, invasive breast cancers [384]. Among the top interacting miRNAs, hsa-mir-93-5p and hsa-mir-1-3p have no role reported in PD pathogenesis, however, hsa-mir-93-5p is involved in epithelial-mesenchymal transition (EMT) in BRCA [403], and hsa-mir-1-3p is documented to regulate BRCA cell progression and metastasis [402]. hsa-mir-106a-5p has been reported to be involved in cognitive improvement in PD brains [404]. hsa-mir-106a-5p is known as a potential biomarker for predicting chemotherapy response and disease prognosis in BRCA [405].

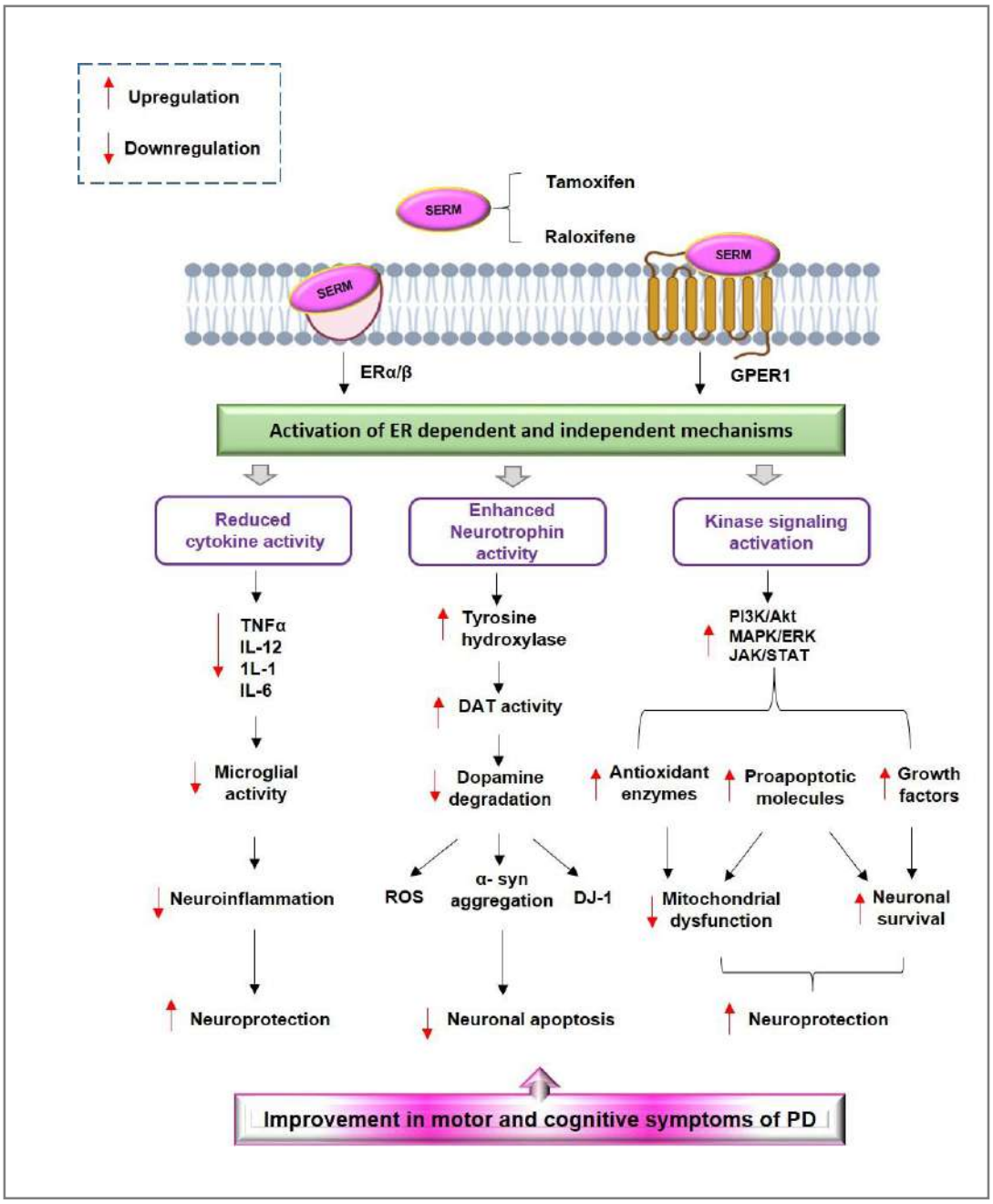


Figure 4.9: Inferred mechanism of action through which selective estrogen receptor modulators (SERM) alleviate symptoms of Parkinson's disease (PD). SERMs can activate both classical estrogen receptors ERα or ERβ and nonclassical transmembrane G protein-coupled ER (GPER1). Via agoinst action, SERMs activate ER independent signaling through various kinases including PI3K/Akt, MAPK/ERK or JAK/STAT kinases which provide neuroprotection by inducing expression of various antioxidant enzymes, proapoptotic molecules and growth factors required for neuronal survival. Similarly, via agonist action at ER-dependent signaling SERMs modulate inflammatory cytokine levels and achieve reduced microglial activity and reduced neuroinflammation. SERMs can enhance neurotrophin activity which in turn induce the expression of tyrosine hydroxylase enzyme and dopamine transporter (DAT) activity. The elevated levels of dopamine can facilitate survival of dopaminergic neurons and alleviate oxidative stress generated by reactive oxygen species and alpha-synuclein aggregation. Red arrows indicate increase (upward) or decrease (downward) in the magnitude of response by SERMs. These pathways can reduce the symptoms related to PD and thus provide neuroprotection.

To dissect the potential role of different therapeutics approved for both the comorbidities, we analyzed the differential gene expression signatures of the approved drugs and compared their concordance scores. Several drugs approved for BRCA were found to produce same expression signatures as PD-related drugs. We found lapatinib, mitoxantrone, neratinib and palbociclib as the top interacting BRCA drugs that have shown positive correlations with the PD drugs. To further elucidate the therapeutic efficacy of these drugs as repurposed drugs for PD, we observed how these drugs mimic or reverse the transcriptomic signatures of PD. The drugs negatively related to PD were considered as possible repurposing drugs. For instance, NDUFV2 was negatively correlated with four BRCA drugs-cyclophosphamide, mitoxantrone, palbocilcib and raloxifene. Several studies have documented the role of NADH dehydrogenase ubiquinone flavoprotein 2 (NDUFV2) gene in PD pathogenesis and the mutations in this gene are responsible for complex I deficiency in PD [416]. The ubiquitin carboxy-terminal hydrolase L1 (UCHL1) gene, a deubiquitinase, is considered as a susceptibility gene for PD [417] and we found three BRCA drugs- doxorubicin, palbociclib and toremifene were able to reverse the effects of UCHL1. Similarly, mammalian seven in absentia homologue-1 (SIAH-1), a RING-type E3 ubiquitin-protein ligase is reported to promote alpha-synuclein aggregation and its ubiquitination [418]. We found three BRCA drugs-olaparib, palbociclib and thiotepa were inversely correlated with SIAH1. Some studies have highlighted the role of an intron variant of methylcrotonyl-CoA carboxylase 1 (alpha) (MCCC1) gene in sporadic PD pathogenesis [419]. Our Cmap analysis reported three BRCA drugs-everolimus, tamoxifene and toremifene were negatively correlated with MCCC1 gene. Furthermore, two BRCA drugs- Lapatinib and Raloxifene were negatively correlated with F-box domain–containing protein (FBXO7) gene that has been known to play a crucial role in parkin-mediated mitophagy and mitochondrial maintenance [420]. We reported olaparib

and thiotepa were inversely related to Farnesyl-diphosphate farnesyltransferase 1 (FDFT1) gene. The exact role of FDFT1 in PD and BRCA parthogenesis is not well known but the gene has been found to promote tumor progression by assisting cholesterol biosynthesis [421]. Mutations in the gene glucocerebrocidase (GBA) gene are considered as an important risk factor in idiopathic PD and the gene affects three pathological pathways alpha-synuclein aggregation, endoplasmic reticulum stress response and autophagic process. We reported two BRCA drugs- doxorubicin and mitoxantrone were inversely correlated with GBA gene signatures. We also found two BRCA drugs- cyclophosphamide and mitoxantrone were reversing SNCA gene signatures, the most critical gene linked with familial PD pathogenesis [422].

To further confirm the repurposing potential of BRCA drugs for PD, we validated the repurposing potential of candidate drugs by CoDReS tool based on their structural and functional properties. The top ranked drugs tamoxifen and raloxifene from CoDReS analysis belong to selective estrogen receptor modulators (SERM) and are approved for estrogen receptor positive metastatic breast cancer and invasive breast cancer, respectively. These modulators act in a tissue specific manner as estrogen agonist or antagonist and many findings have suggested that SERMs including tamoxifen and raloxifene might exert beneficial effects in PD [423]. From literature analysis, we found that raloxifene has already shown neuroprotective effects in PD. Numerous studies have identified the role of raloxifene in reducing dopaminergic cell death in PD models and restoring dopamine levels [424]. However, there is no direct literature support available for the neuroprotective behaviour of tamoxifen in PD. A study by D'Astous et al. have reported that tamoxifen shows neuroprotective behaviour against methamphetamine and MPTP-induced toxicity when used without estrogen [425]. On contrary, a study has claimed that tamoxifen therapy

might disrupt the neuroprotective effect of estrogen and is associated with increased risk of PD [426].

We proposed that both tamoxifen and raloxifene can activate different estrogen receptor-dependent and independent mechanisms to provide neuroprotection including reduced neuroinflammation, enhanced dopaminergic signaling and reduce neuronal apoptosis. The proposed mechanism of action is summarized in **Figure 4.9**. To conclude, our study is the first to establish a common crosstalk between PD and BRCA based on multi-omic analysis. Our findings will provide a mechanistic platform for a better understanding of the molecular link between PD and cancer. We also proposed the repurposing of SERM drugs for PD treatment; however, experimental studies are warranted to justify their repurposing potential.

4.4 KEY HIGHLIGHTS OF THE STUDY

- ✓ Transcriptional and post-transcriptional regulatory signatures common between PD and BRCA
- ✓ Electron transport chain and oxidative phosphorylation as enriched pathways common between PD and BRCA.
- ✓ SERMs reverse neuroinflammation and modulate dopaminergic signaling pathways in PD pathogenesis
- ✓ Raloxifene and tamoxifen as putative therapeutic agents in PD pathology
- ✓ Raloxifene and tamoxifen alleviate PD pathogenesis through modulating estrogen receptor signaling

CHAPTER V

IN SILICO MOLECULAR DOCKING AND SIMULATION STUDY TO IDENTIFY REPURPOSED MAOB INHIBITORS FROM THE POOL OF FDA-APPROVED ANTICANCER DRUGS

CHAPTER V: *IN SILICO* MOLECULAR DOCKING AND SIMULATION STUDY TO IDENTIFY REPURPOSED MAOB INHIBITORS FROM THE POOL OF FDA-APPROVED ANTICANCER DRUGS

5.1 INTRODUCTION

PD is a recognizable neurodegenerative condition with a wide range of causes and clinical manifestations. Oxidative stress is one of the widely accepted hypothesis of PD pathogenesis that contributes to the degeneration of dopaminergic neurons. However, since last few decades, no revolutionary treatments have been developed for PD, modulation of the dopaminergic system is the most effective treatment available. The monoamine oxidases are FAD (Flavin adenine dinucleotide)-dependent enzymes that catalyze the metabolism of monoamine neurotransmitters including dopamine, serotonin, adrenaline and noradrenaline and oxidative deamination of intracellular arlyalkyl amines. Monoamine oxidases (MAO) exist in two different isoforms (MAOA and MAOB), both of them differ in substrate specificities and the selectivity of inhibitors (Robakis and Fahn 2015). MAOA is mainly expressed in the intestinal tract while the MAOB enzyme is predominantly found in the brain, where it converts exogenous and endogenous dopamine to hydrogen peroxide, an essential process associated with oxidative insult in PD (L and L 2017). As brain neurotransmitter levels are related to the pathologies of various neurological indications, inhibition of MAO emerged as a promising therapeutic option.

Substantial evidence and experimental clinical trials have justified the neuroprotective potential of different MAO inhibitors for PD. Various forms of MAOB inhibitors have already been marketed for PD including, irreversible selective inhibitors (Selegiline, Rasagiline) and reversible inhibitors (Safinamide). Although, the symptomatic effects of MAOB inhibitors are limited, still, their disease-modifying effects and safety profile make

them ideal therapeutic options for early PD treatment (Löhle and Reichmann 2011). Recently, efforts have been made to develop new selective and reversible MAOB inhibitors with limited side effects. To overcome the main drawbacks of MAOB inhibitors, including selectivity and irreversibility, continuous efforts are attempted to develop novel potent inhibitors. Recently, cheminformatics and *in silico* tools have facilitated rational drug design process to guide drug-target interactions and selection of best candidates. Drug repurposing is the simplest approach used to identify novel applications of the drugs already available in the market. Compelling evidence have reported the role of MAO in tumor progression and metastasis and MAO inhibitors represent anticancer potential (Aljanabi et al. 2021). The dual role of MAO inhibitors in neuroprotection as well as tumor inhibition provides a basis of the repurposing of anticancer drugs as MAO inhibitors in PD. The current repurposing study was designed to develop new MAOB inhibitor drugs from the pool of FDA-approved anticancer drugs. Since BBB permeation is an important parameter of the neuroprotective drugs and early prediction of BBB permeability reduces the chances of pharmacokinetic failure. In experimental trials, the anticancer drugs were first subjected to BBB analysis. The interaction of various BBB permeable anticancer drugs with MAOB was analyzed by molecular docking and simulation approach.

5. 2. COMPUTATIONAL METHODS

5.2.1 DATA SOURCE

Within this research, the list of FDA-approved anticancer drugs was retrieved from Cancer.gov, the central website for the NCI. The information related to all the drug combinations was excluded and the drugs for which molecular structures were available, were included in the study.

5.2.2 LIGAND SIMILARITY SEARCH

To quantify the similarity between query ligands (drugs) and template ligand (safinamide), we exploited LS-align tool. The tool performs structural alignment of ligands relative to random ligand pairs based on inter-atom distance and chemical bond comparisons [427].

5.2.3 BBB PERMEABILITY ANALYSIS

The FDA-approved anticancer drugs having structural alignment with safinamide were analyzed for their blood-brain barrier permeability by using online BBB prediction server-Cbligand. It is a free web tool to predict BBB permeation of small molecules [428].

5.2.4 MOLECULAR DOCKING STUDIES

The crystal structure of human protein MAOB in complex with the selective inhibitor safinamide (PDB accession no: 2V5Z) with the resolution of 1.60 Å was extracted from Protein data bank (PDB) website. Study of receptor-ligand docking was conducted with Autodock vina [429] with a box size of 30 x 30 x 30. To obtain a clean protein structure, functional ligands, water molecules were removed from the Structure of human MAO B. Accurate prediction of active sites is an important tool in bioinformatics. In this study, the active sites were predicted by using Biovia Drug discovery studio visualizer 2020.

5.2.5 MOLECULAR DYNAMICS SIMULATION

Dynamic studies were conducted on complex files with the best binding energy. A molecular dynamics simulation of a selected protein-ligand complex was performed with Gromacs-2019.4 [430]. The forcefield coordinates were obtained by downloading the ligand topology from the Prodrug server. A steepest descent algorithm was used for pre-processing the system using 1500 steps of vacuum minimization. A water simple point charge (SPCE) water model was used to solvate the complex structures in a cubic periodic box of 0.5 nm. Following this, the salt concentration of the complex systems was maintained at 0.15 M using a suitable number of Na+ and Cl- counterions. It was based on

the results of a previously published paper that the system preparation took place. The final production run of each structure from the equilibration phase was conducted using an ensemble of NPT (Number of atoms in the system, pressure of the system and temperature of the system) simulations for 100 ns. An analysis of trajectory was conducted using the root mean square deviation (RMSD), root mean square fluctuation (RMSF), Radius of gyration (Rg) and H-Bond simulation packages in Gromacs.

5.2.6 MOLECULAR DYNAMICS AND FREE ENERGY CALCULATION (MM-PBSA)

Molecular Mechanics Poisson-Boltzmann surface area (MM-PBSA) approach was employed to understand the binding free energy (ΔG binding) of an inhibitor with protein over simulation time. A GROMACS utility g_mmpbsa was employed to estimate the binding free energy. To obtain an accurate result, we computed ΔG for the last 20 ns with 1000 frames. The net energy of the system was calculated as

$$\Delta Gbinding = Gcomplex - (Gprotein + Gbinding)$$

5.2.7 ANALYSIS OF PHYSICOCHEMICAL PARAMETERS, ADMET AND TOXICITY PROFILE PREDICTION

The prediction of various physicochemical parameters and ADME (absorption, distribution, metabolism, excretion) properties was done by online tool SwissADME [325] and toxicity profiling was performed by Pro-Tox server [431].

The workflow of all the methods is provided in **Figure 5.1**

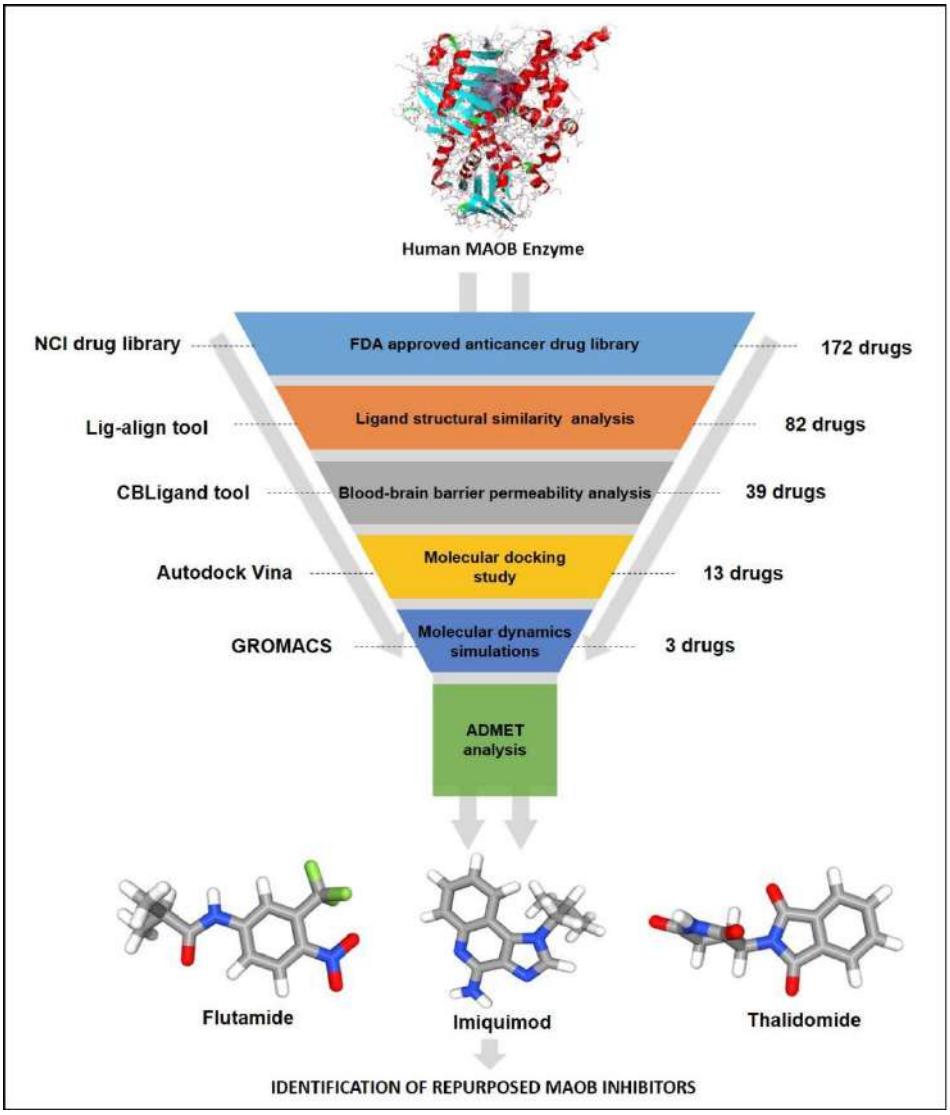


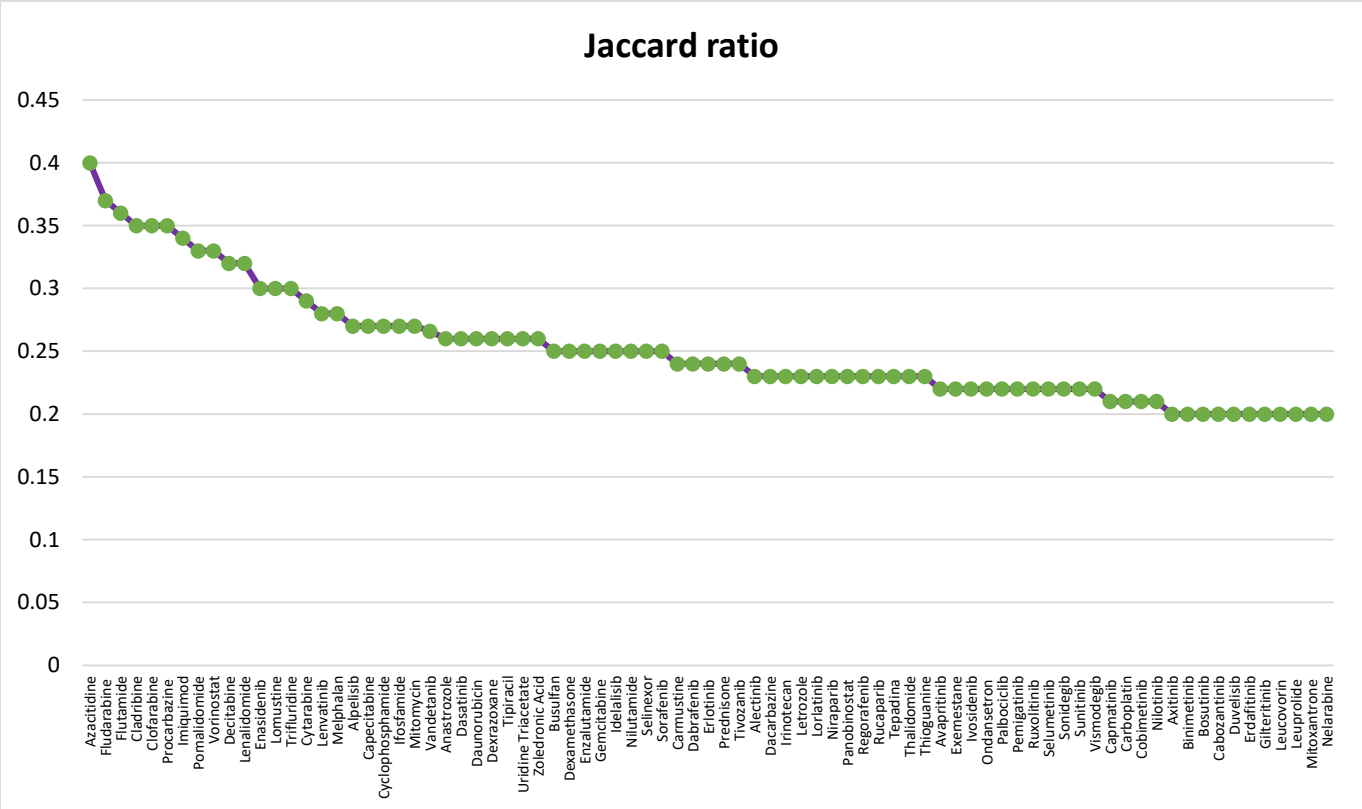
Figure 5.1: Workflow of repurposing of FDA-approved anticancer drugs against MAOB enzyme. The FDA approved anticancer drug library had 172 drugs. these drugs were first filtered based on ligand structural similarity analysis that resulted in 82 drugs. BBB permeability analysis identified 39 drugs that were able to cross BBB. The molecular docking analysis of these 39 drugs identified 13 drugs interacting with MAOB active site. The molecular dynamics simulations analysis of top hits resulted in the identification of potent MAOB inhibitors

5.3 RESULTS

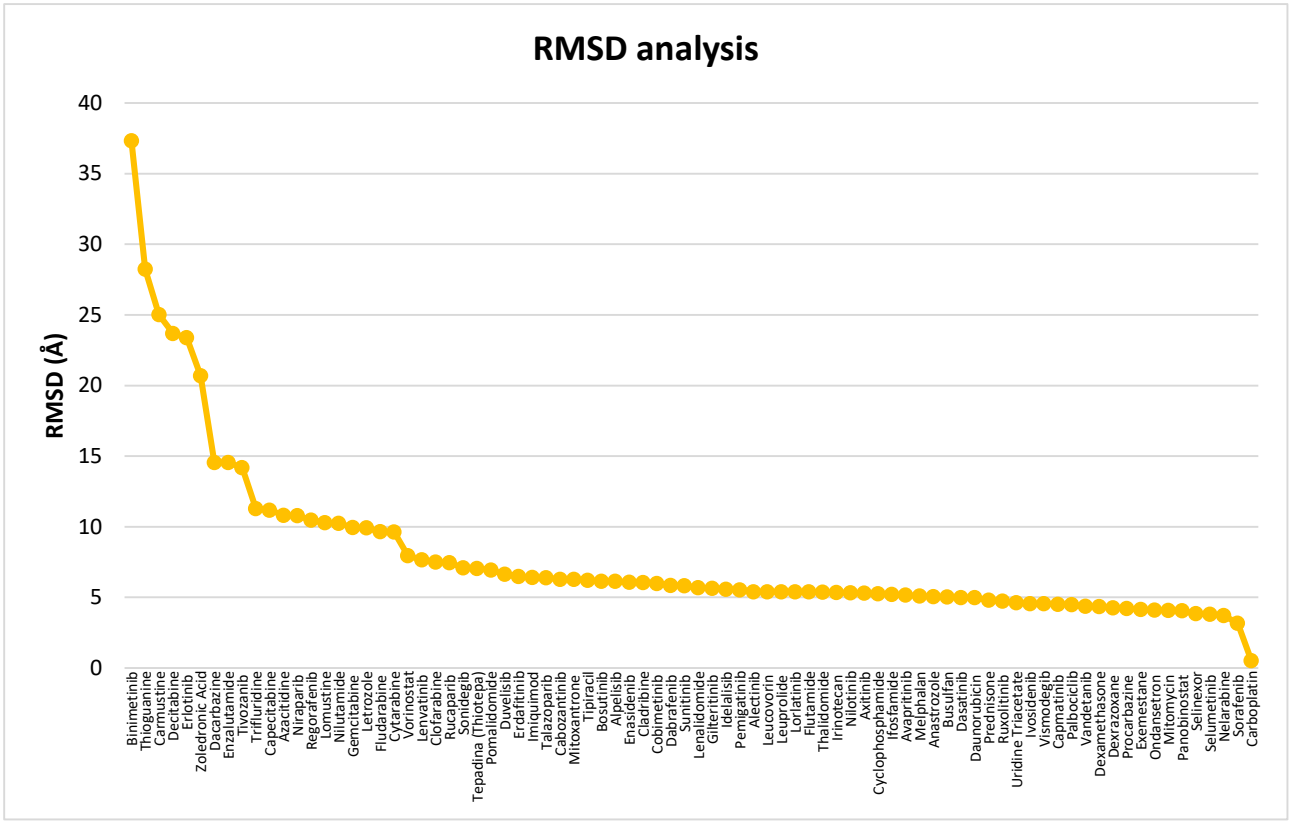
5.3.1 IDENTIFICATION OF TEMPLATE LIGANDS BY STRUCTURAL ALIGNMENT

The FDA-approved anticancer drug library includes 172 drugs approved for various cancer indications. We performed a structural alignment of 172 drugs with the reference drug safinamide. We identified the structurally aligned drugs based on Jaccard ratio and RMSD values. Jaccard similarity index is a measure of similarity of chemical bonds between two

molecules. We selected 82 drugs having a Jaccard ratio >0.2 and also observed their RMSD values to know the structural deviation from the query ligand. We found that the average value of the Jaccard ratio was 0.25 and the average RMSD was 7.8. The distribution of the Jaccard ratio and RMSD values for different drugs has been shown in **Graphs 5.1 and 5.2,** respectively. The highest value of the Jaccard ratio was 0.4 for azacytidine while the lowest value was 0.2 for 12 drugs namely- axitinib, binimetinib, bosutinib, cabozantinib, duvelisib, erdafitinib, gilteritinib, leucovorin, leuprolide, mitoxantrone, nelarabine, and, talazoparib. Likewise, the highest deviation was observed for binimetinib (37.33Å) and lowest was for carboplatin (0.52Å).



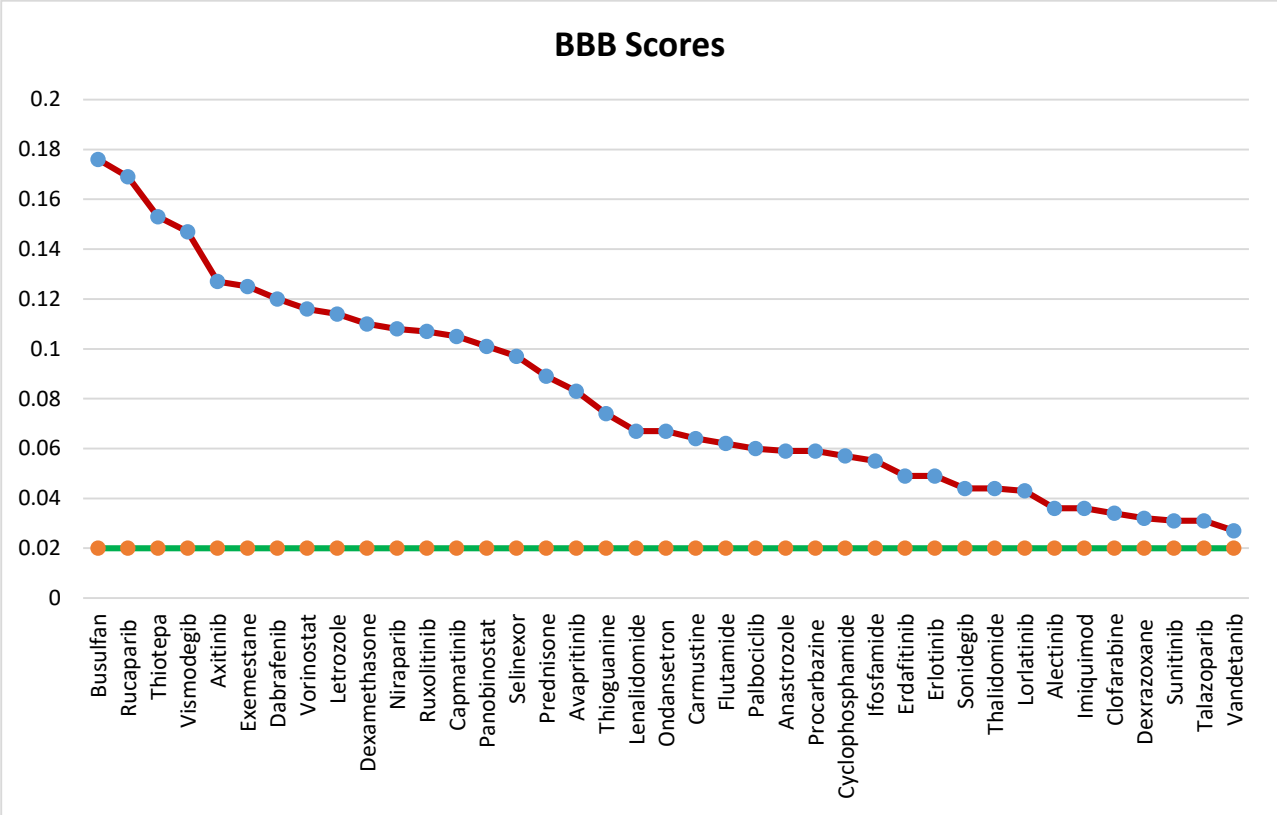
Graph 5.1: Jaccard ratio of the anticancer drugs as calculated from LS-align tool. Out of 172 drugs, 82 drugs were found to be structurally similar to the reference drug safinamide. The value of the Jaccard ratio varies from 0.2 to 0.4.



Graph 5.2: Graphical representation of RMSD values of different anticancer drugs as calculated by LS-align tool. The value ranges from 0.52 to 37.33. Higher RMSD values represent more structural deviation from the reference drug structure.

5.3.2 BBB PERMEABILITY ANALYSIS

BBB permeability analysis found out of 82 drugs from the previous step, 39 drugs were able to cross BBB and can be used as input drugs for docking analysis. The BBB scores of various drugs varies from 0.027 to 0.176 with busulfan showing the highest score and vandetanib showing the lowest score as shown in **Graph 5.3.**



Graph 5.3: Graphical representation of BBB scores of various drugs as analyzed by CBLigand tool. The threshold value was taken 0.02 and all the drugs having BBB scores above this range were considered as BBB permeable. Only BBB permeable drugs are represented in the graph.

5.3.3 MOLECULAR DOCKING AND IDENTIFICATION OF BINDING PATTERNS

All 39 BBB penetrant anticancer drugs were docked against MAOB and ranked according to their docking scores. Out of 39 drugs, only 21 drugs have shown interaction with MAOB active site. The docking scores of all the compounds were shown in **Annexure 5.** Out of 21 drugs, 8 drugs have shown positive docking scores while the rest 13 drugs have actually interacted with negative scores. We found that most of the drugs reported docking scores in the spectrum of -3 to -8 kcal/mole. For further analysis, we selected 3 anticancer drugs based on their binding affinities and favorable binding interactions. Imiquimod, a drug approved for basal cell carcinoma exhibited the best docking score (-8.5 kcal/mole). Similarly, thalidomide which has been approved for multiple myeloma and flutamide

approved for prostate cancer have shown docking scores of -8.1 kcal/mole and -8.0 kcal/mole, respectively.

Table 5.1: Docking scores and summary of the interactions involved for the top 3 docked drugs with MAOB

S.No.	Drug name	Docking scores	Hydrogen bond interactions	Other interactions
1	Safinamide (SUF)	-6.1Kcal/mole	**Cys172, Gln206, Tyr435 (H-bond)** **FAD (C-H bond)**	Tyr398 (alkyl) Leu171, Ile198 (pi-alkyl) Tyr60, Phe168, Ile199, Tyr326, Leu328, Phe343 (Van der Waals)
2	Flutamide (D22)	-8 Kcal/mole	**Gln206, FAD** (H-bond) **Tyr435** (Pi-donor H-bond)	Tyr60, Phe168, Leu171, Ile199, Tyr326, Phe343 (alkyl) Cys172 (Pi-sulfur) Tyr398 (Pi-Pi stacked)
3	Imiquimod (D27)	-8.5 Kcal/mole	**Cys172** (H-bond)	Leu171, Ile198, Tyr398, FAD (Pi-alkyl) Tyr435, FAD (Pi-sigma) Tyr435 (Pi-Pi stacked) Cys172 (Pi-sulfur) Tyr60, Phe168, Ile199, Gln206, Tyr326, Leu328, Met341, Phe343 (Van der Waals)
4	Thalidomide (D44)	-8.1 Kcal/mole	**FAD** (H-bond)	Leu171 (Pi-sigma) Cys172 (Pi-sulfur) Tyr326 (Pi-Pi stacked) Tyr60, Phe168, Ile199, Gln206, Leu328, Phe343, Tyr398, Tyr435 (Van der Waals)

***Common H-bond interactions are highlighted in bold**

The docking poses of top 3 drugs are presented in **Table 5.1**. From the conformational viewpoint, the substrate binding site of MAO-B consists of the FAD cofactor, an "aromatic box" defined by two flanking residues Tyr398 and Tyr435, and some other critical residues such as Tyr60, Cys172, Tyr326, Met341, Ser200, Gln206 and Thr314. Additionally, Phe168, Ile199 and Ile316 are reported as critical residues for MAOB selectivity (Binda et

al. 2011). Previous studies have reported that amino acid residues, Phe168 and Ile316, are responsible for establishing van der Waals and electrostatic interactions with MAOB interacting compounds. The structure of MAOB with FAD and the docked complex with SUF are presented in **Figure 5.2.**

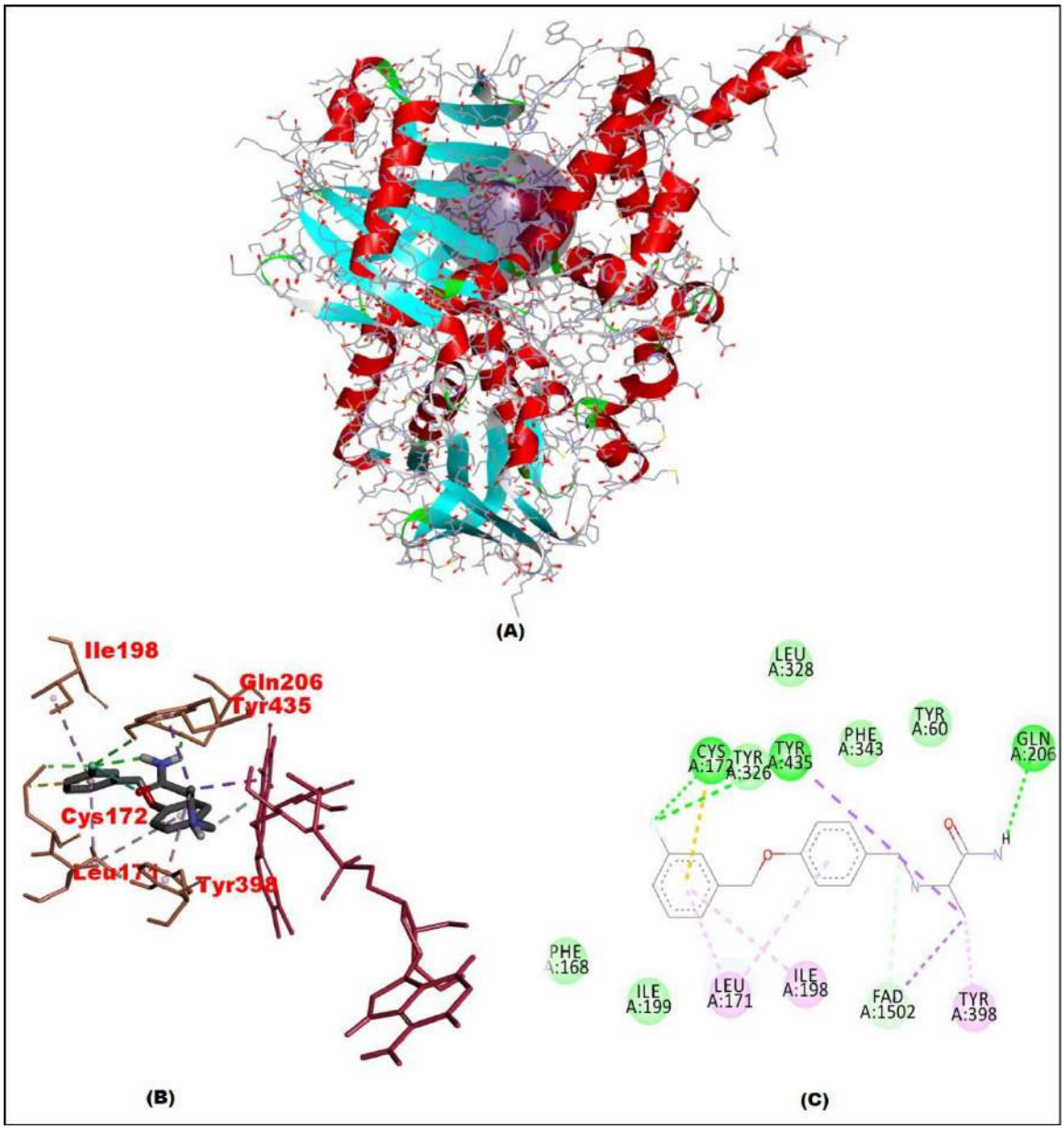


Figure 5.2: (A) Crystal structure of human monoamine oxidase B enzyme (PDB ID: 2V5Z) in complex with FAD cofactor. The binding site of MAOB is shown in purple ball. (B) 3D structure of docked MAOB with the reference drug safinamide. FAD is shown in pink color. (C) 2D interactions of MAOB with safinamide representing H-bonding and other non-polar interactions

We observed that flutamide had two conventional H-bond interactions (residues Gln206 and FAD) with MAOB, imiquimod had one H-bond involving Cys172 residue and thalidomide also had one H-bond interaction with FAD. Importantly, we found that not thalidomide, but both flutamide and imiquimod interacted with Tyr398 and Tyr435. Moreover, the complex of MAOB had 7 hydrophobic interactions with flutamide involving residues Tyr60, Phe168, Leu171, Cys172, Ile199, Tyr326, and Phe343, had 3 hydrophobic interactions with thalidomide involving residues Leu171, Cys172 and Tyr326 and had 4 hydrophobic interactions involving Leu171, Cys172, Ile198, FAD with imiquimod. Additionally, thalidomide and imiquimod had Van Der Waals interactions with the MAOB complex as summarized in **Table 5.1**. All three drugs were situated in the aromatic cage enclosed by the FAD ring and adjacent residues of the MAOB active site (**Figure 5.3**).

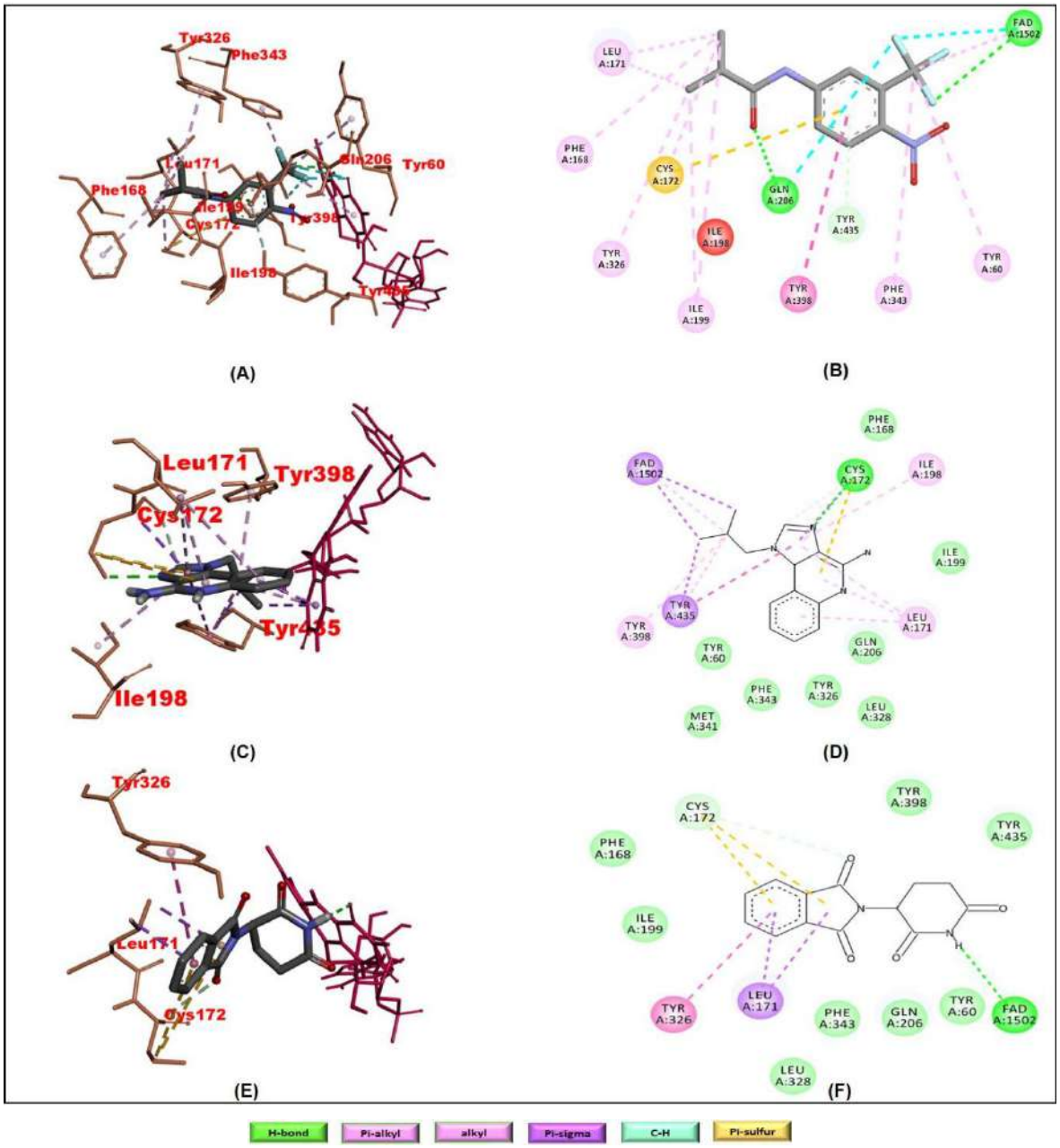


Figure 5.3: Structural representations of 3D and 2D interactions of MAOB protein with anticancer drugs (A) & (B) flutamide, (C) & (D) imiquimod, and (E) & (F) thalidomide. FAD is presented in green color. All the interacting residues are presented in different colors as shown in the color bar.

5.3.4 MOLECULAR DYNAMICS SIMULATIONS AND DETERMINATION OF STRUCTURAL CONFORMATIONS AND STABILITY

Docking alone cannot provide a complete insight of binding and dynamics of the drugs with protein, so, simulations were performed using the 3D structures of human MAOB in complex with the selective inhibitor safinamide (2V5Z), APO and complexes with selected

ligands derived from dockings using FAD, FAD-D22, FAD-D27, FAD-D24 and FAD-SUF. MD simulations were performed for 100 Nanoseconds (ns), to understand the stability of the above-mentioned protein-ligand complexes including RMSD (Root Mean Square Deviation), RMSF (Root Mean Square Fluctuations), RG (Radius of Gyration), and H-Bonds (Hydrogen bonds) calculations. RMSD is a statistical measure of predicting the stability of the protein over the time during the simulations. The RMSD from the **Figure 5.4 (A)** shows that from 40 to 100 ns, APO, FAD, FAD-D27, FAD-D44, FAD-D22 and FAD-SUF proteins exhibit stability over the time. We found that thalidomide has shown a great fluctuation from 0.15 to 0.54 nm. However, both flutamide and imquimod have exhibited more stability and less fluctuations over the simulation period.

RMSF analysis determines which amino acids of the protein are fluctuating more, resulting in the destabilization of the protein. The RMSF values were calculated against the simulation timescale of 0 to 100ns for APO and its complex with FAD, FAD-D27, FAD-D44, FAD-D22 and FAD-SUF are depicted in **Figure 5.4 (B)** It was evident from the figure that thalidomide has shown a very less residue fluctuation during the whole simulation period. However, there were variable peaks in residue positions 465-471 for flutamide, in positions 460-465 for imiquimod, and at 466-471 for thalidomide. The fluctuations were higher for all three drugs at residues 494-501.

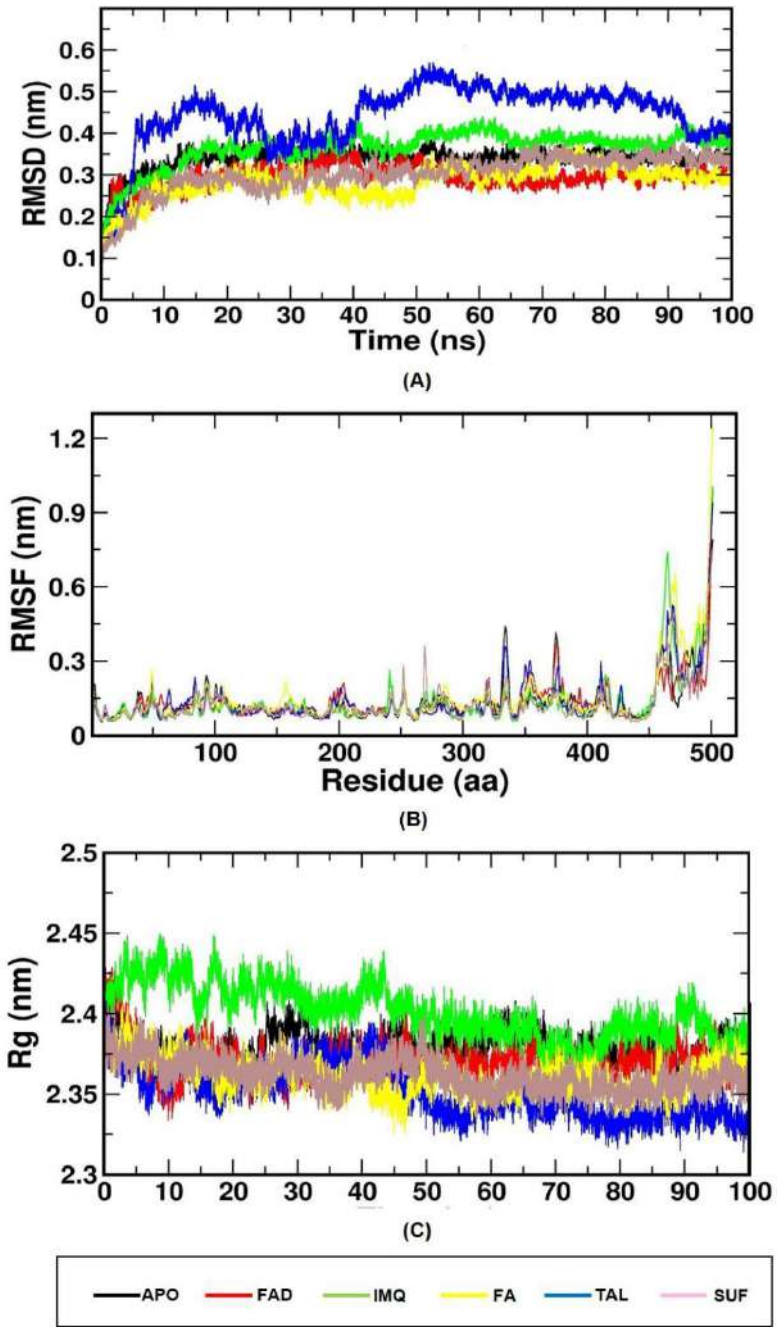


Figure 5.4: (A) Root mean square deviation (RMSD) analysis of protein, reference drugs and test drugs. RMSD of all the components falls under the acceptable range of 0.3nm except for thalidomide and imiquimod. Thalidomide is showing the highest deviation. (B) Root mean square fluctuation (RMSF) analysis of all the drugs, with FAD and protein. The fluctuations are observed based on the intensity of the individual peaks. The highest fluctuation was observed for flutamide at residues 494-501. (C) Radius of gyration (Rg) analysis of all the drugs along with protein and FAD. The highest variation was observed for imiquimod. All the systems had less Rg values after 45ns time period. The representative colors of all the systems are presented in color bars. APO: protein; FAD: FAD cofactor; IMQ: imiquimod; FA: flutamide; TAL: thalidomide; SUF: safinamide

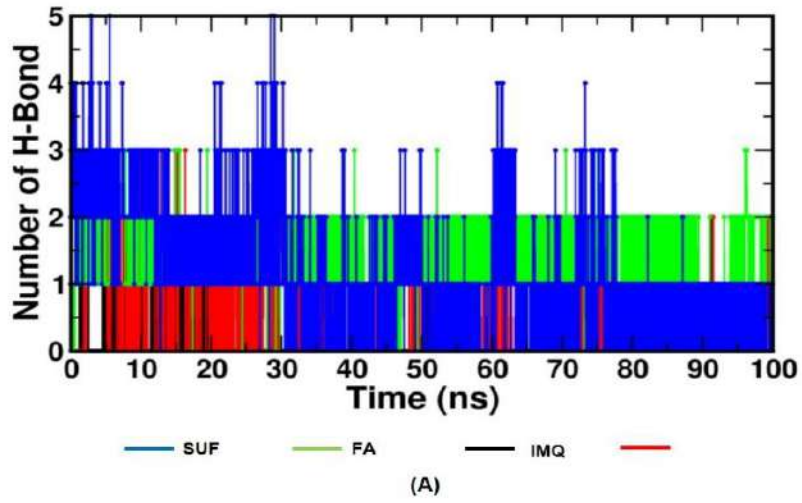
The Rg determines the distribution of all the atoms in a molecular structure with respect to its center of mass. The value represents the compactness of the protein. The Rg values in

Figure 5.4 (C) indicate that imiquimod had more swirls in comparison to the protein itself, however, after 45 ns time interval, the Rg value did not change significantly with respect to the protein. The other two compounds flutamide and thalidomide had fewer structural swirls than the protein. It has been noted that after 45 ns time interval, all the three drugs had less Rg values indicating that the protein is not undergoing major structural change when bound to the drugs.

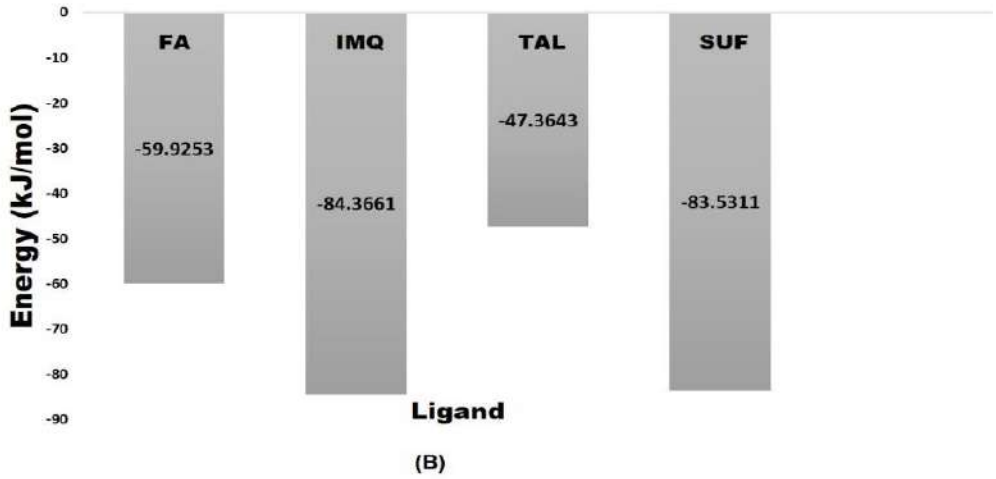
5.3.5 H-BOND INTERACTIONS AND MMPBSA

H-bonds play a prominent role in determining the specificity and stability of protein-ligand binding (Wade and Goodford 1989). The presence of H-bond interactions in the docked complexes were identified by gmx H-bond tool. The H-bond plot of the simulation was presented in **Figure 5.5 (A).** The maximum number of H-bonds were three for flutamide, two for thalidomide and one for imiquimod.

The molecular mechanics energies combined with the Poisson–Boltzmann and surface area continuum solvation (MM/PBSA) is a method to evaluate the free energy of binding or affinity of small ligands to the target biomolecules. The comparative binding energies are presented in **Figure 5.5 (B).** As can be seen, imiquimod had better binding energy as compared to safinamide while flutamide and thalidomide had lesser binding energy values.



(A)



(B)

Figure 5.5: (A) Hydrogen bond interactions for all the drugs alongwith the reference drug. No of H-bonds are three for safinamide, and flutamide, two for thalidomide and one for imiquimod. (B) The molecular mechanics energies combined with the Poisson–Boltzmann and surface area continuum solvation (MM/PBSA) shows that only imiquimod has highest interaction energy as compared to the reference drug.

5.3.6 PHYSICOCHEMICAL AND ADMET PROPERTIES IN ACCORDANCE WITH THE RULES OF DRUG-LIKENESS

The prediction of physiochemical parameters and determination of ADMET properties are considered crucial factors in the drug development process. Various physicochemical features including molecular weight (MW), number of hydrogen bond donors (HBD) and acceptors (HBA), number of rotatable bonds, and topological polar surface area (TPSA) were estimated for flutamide, imiquimod and thalidomide and presented in **Table 5.2**. In

keeping with the rule of five, all the three drugs were in accordance with the set parameters and no violation was found. Likewise, the ADME parameters including water solubility, octanol/water partition coefficient (log P), gastrointestinal absorption, and others were found to be suitable. The toxicity (hepatotoxicity, immunogenicity and mutagenicity) analysis has shown that all three drugs have a moderate risk of toxicity. Thalidomide is not associated with any kind of toxicity risk while the other two drugs are associated with one or more toxicity classes.

Table 5.2: ADME properties and toxicity parameters of the ligands as calculated from Swiss ADME and Pro-Tox servers

ADME properties	Flutamide	Imiquimod	Thalidomide
MW	276.21g/mol	240.30 g/mol	258.23 g/mol
RB	5	2	1
HBA	6	2	4
HBD	1	1	1
TPSA	74.92	56.73 Å²	83.55
Water solubility	soluble	soluble	very soluble
XLOGP	3.35	2.62	0.33
WLOGP	4.17	2.83	-0.67
MLOGP	2.03	2.96	1.28
GI absorption	high	high	High
P-gp substrate	no	yes	No
CYPA12 inhibitor	yes	yes	No
CYP2C19 inhibitor	yes	no	No
CYP2C9 inhibitor	no	no	No
CYP2D6 inhibotor	no	no	No
CYP3A4 inhibitor	no	no	No
Skin permeation, Log Kp	-5.61 cm/s	-5.91 cm/s	-7.64 cm/s
Lipinski's rule	yes	yes	Yes
Bioavailability score	0.55	0.55	0.55
Toxicity class	moderate	moderate	Moderate
LD50	550mg/kg	300mg/kg	113mg/kg
Hepatotoxicity	yes	no	no
Immunogenicity	no	no	no
Mutagenicity	yes	yes	no

5.4 DISCUSSION

Among all antiparkinsonian agents, the MAOB inhibitors are of the greatest interest as they provide versatile neuroprotective functions with specific activity against dopamine metabolism (30160213). Safinamide is the prototype of the new generation of MAOB inhibitors with reversible mechanisms of action. A number of studies have been published to identify novel safinamide based reversible MAOB inhibitors. In a recent study, Crisan, Luminita et al. have found fenamisal and monobenzone as repurposed MAOB inhibitors by virtual screening and molecular docking based experiments (33237524). Still, little attention has been paid on the repurposing aspect to find MAOB inhibitors. A plethora of studies have reported the neuroprotective properties of anticancer drugs and justified their repurposing potential as well (PMC6027455) (32853752). The aim of the current study was to identify repurposed MAOB inhibitors from the currently marketed anticancer drugs. We extracted the information of currently marketed anticancer drugs and filtered them for their BBB permeability. Among 172 anticancer drugs, 77 drugs were able to cross BBB and thus can be considered as effective CNS drugs in clinical settings. The BBB permeable anticancer drugs were further subjected to molecular docking analysis to explore their binding interactions with MAOB enzyme. The information on the active site and residues involved in binding with safinamide was collected from the literature and the reference drug was allowed to be redocked with the target enzyme. As reported, the MAOB enzyme active site comprises a hydrophobic cavity (volume is 420) and an entrance cavity (volume is 290). It has been shown that Phe103, Phe104, Trp119, Leu164, Leu167, Phe168, Leu171, Ile199, Ile316, and Tyr 326 residues cover the entrance cavity. Residue Ile199 is very critical as it acts as a gateway and allows access for the substrate/inhibitor accompanied by the movement of loop 99-112. Molecular docking analysis revealed that out of 77 drugs, only 40 drugs were successfully docked to MAOB active site. The top three drugs with

highest docking score were further evaluated for binding interactions. The analysis of interacting residues has shown that all the three drugs bind in the active site of the enzyme near the FAD cofactor. It was clear from the 2D diagram that in flutamide there was formation of two hydrogen bonds, a halogen bond and different hydrophobic bonds. The oxygen of carbonyl group formed a H-bond with Gln206 and the fluoride atom of trifluoromethyl formed H-bond with FAD cofactor. Similarly, for imiquimod, we found that a single H-bond was there in between imidazole nitrogen and Cys172 residue. Apart from this, benzene ring, aminopyrimidine ring and imidazole ring were involved in different types of hydrophobic interactions. Also, the two methyl groups were interacting with FAD cofactor by hydrophobic (pi-sigma) interaction. For thalidomide, we observed that a single H-bond interaction was present between the nitrogen atom of dioxo piperidine ring with FAD cofactor. The heterocyclic isoindole ring formed different types of hydrophobic interactions. Therefore, we noticed that in any way all three drugs were interacting with the crucial residues mentioned previously for MAOB binding.

To confirm the stability of the docked complexes, molecular dynamics simulations were performed for 100ns. We applied RMSD analysis to estimate the stability of protein-ligand complexes and the apoprotein. It has been reported that a maximum fluctuation of 3Å (0.3nm) is acceptable to indicate system equilibrium. We observed that only thalidomide had appreciable fluctuations during the simulation period, whereas both flutamide and imiquimod showed stability. To further complement the docking results, RMSF and Rg analyses were carried out. RMSF analysis results have shown that residues interacting with protein fluctuated less during the time period of simulation. The higher Rg value is indicative of the labile nature of the complexes, while the lower value correlates with the constant nature of the complexes [432]. It has been clear from the Rg plot that both imiquimod and flutamide had more or less fluctuation, however, flutamide had maintained

a steady-state. Furthermore, H-bond interactions are considered as the most stable and ubiquitous in different biological systems for both ligand binding and enzyme catalysis. The H-bond interaction simulation plot indicated that both imiquimod and thalidomide formed one H-bond with the enzyme while flutamide had two H-bond interactions. Adding more to the analysis, we calculated the binding energies of the three drugs with the enzyme with respect to the reference drug. The MMPBSA analysis had shown that only imiquimod had better binding energies than the reference drug, suggesting that it can be a good hit in the identification of novel MAOB inhibitors.

Apart from structural analysis, investigation of clinical safety parameters is one of the most crucial aspect of drug development. We performed SWISS ADME analysis of all three proposed drugs for pharmacokinetic properties and ADME parameters. In accordance with the literature studies, for optimum brain penetration drugs should have molecular weight <450, log P<5, number of H-bond donors<3, number of H-bond acceptors<7, number of rotatable bonds<8, and total polar surface area (TPSA)>60-70$Å^2$ [433]. All three drugs have good pharmacokinetic properties and followed Lipinski's rule of five. Besides, toxicological parameters need to be verified for a drug nominee to become a successful marketed drug. We analyzed the drugs for their toxicological, mutagenic and immunogenic effects. We found that thalidomide was not associated with any adverse effect while imiquimod was found to be mutagenic and flutamide was both hepatotoxic and mutagenic.

From literature analysis, it was found that imiquimod is a TLR (toll-like receptor) agonist which modifies the immune response and induces apoptosis in cancer cells [434]. However, no study has reported the neuroprotective potential of this drug. Likewise, flutamide is a nonsteroidal antiandrogen known to block the action of exogenous and endogenous testosterone. It has been reported that flutamide may enhance the neuroprotective effects of testosterone and reverse neurological impairment in the experimental cerebral ischemia

model [435]. Moreover, a study has demonstrated that flutamide alleviated testosterone induced neurotoxicity in dopaminergic cell lines by inhibiting caspase-3 activity [436]. Thalidomide is an anticancer drug with immunomodulatory and anti-inflammatory properties which inhibit the activity of various inflammatory cytokines. In the experimental PD model, it has been shown that thalidomide improved MPTP-induced neurotoxicity by increasing dopamine contents and reducing MAOB levels [437]. All the aforementioned studies supported the hypothesis of repurposing anticancer drugs for PD treatment.

5.5 KEY HIGHLIGHTS

- ✓ Anticancer drugs as repurposed monoamine oxidase inhibitors for Parkinson's disease.
- ✓ Molecular docking analysis identified the interactions of anticancer drugs flutamide, imiquimod, and thalidomide with MAOB.
- ✓ Molecular dynamics simulations studies confirmed the repurposing potential of imiquimod.

CHAPTER VI

NATURAL PRODUCTS AS REPURPOSED DRUGS AGAINST COMMON TARGETS FOR ALZHEIMER'S AND PARKINSON'S DISEASE

CHAPTER VI: NATURAL PRODUCTS AS REPURPOSED DRUGS AGAINST COMMON TARGETS FOR ALZHEIMER'S AND PARKINSON'S DISEASE

6.1 INTRODUCTION

AD and PD are the two most debilitating NDDs that share common pathological events such as abnormal protein aggregation, oxidative stress, inflammation, aging and progressive neuronal death [438]. In addition, deregulation of enzymatic activity mediating diverse cellular processes is another commonality and several enzymes have been implicated in the pathogenesis of both AD and PD. Prominent among these enzymes are-cyclin-dependent kinases (CDKs), and glycogen synthase kinases (GSKs). CDK5 is predominantly expressed in the post-mitotic neurons having multiple roles in synaptic functions and neuronal functioning. In AD, CDK5 contributes to the development of neurofibrillary tangles by aberrantly inducing tau phosphorylation [439]. Similarly, in PD mouse model, CDK5 dysregulation was correlated with dopaminergic neuronal loss and CDK5 inhibition reduced neuronal death [245]. Likewise, GSK-3β has important brain functions such as maintaining brain homeostasis, neuronal growth and differentiation, and modulation of neuronal apoptosis. In AD, GSK-3β levels are found to be high and it is the main tau kinase involved in tau hyperphosphorylation. It is also associated with NMDA receptor activation, neuroinflammation, regulation of β-catenin signaling, and activation of different transcription factors [440]. In PD brains, GSK-3β levels were found to be higher in nigral pigmented neurons, where it promotes Lewy body formation by promoting α-synuclein phosphorylation and aggregation [441].

Current therapeutics available for the treatment of NDDs are limited and offer only symptomatic benefits. Therefore, numerous studies have focused on the identification of novel therapeutic for AD and PD, individually, however, few have investigated the

common therapeutic targets. Plant-derived products, including flavonoids, phenols, alkaloids and terpenoids have been recognized since ancient times for the treatment of various ailments. Phytochemicals are considered promising candidates for treating NDDs and known to provide neuroprotection against excitotoxicity, neuroinflammation, and oxidative stress [442] . Butyrolactone, indirubins, flavopiridol are the known CDK5 inhibitors with neuroprotective properties [443] while indirubin analogs such as 6-bromoindirubin, alsterpaullone, aloisine A, maleimide inhibitors are some of the natural compounds investigated as GSK-3β inhibitors for CNS disorders [444]. However, the currently available CDK5 and GSK-3β inhibitors failed to show promising results in clinical trials and thus demand further investigation.

Therefore, in this study, we evaluated the anti-Alzheimer's and anti-Parkinson's activity of the selected natural compounds against the two common enzymes associated with AD and PD. We screened a library of anticancer natural compounds that have already been investigated for different cancers and then analyzed their interaction with the selected enzymes using molecular docking and simulations approach.

6.2 MATERIALS AND METHODS

6.2.1 DATA SOURCE

Within this research, a list of natural compounds with anticancer properties has been prepared from literature studies available on Pubmed for the last five years.

6.2.2 BBB PERMEABILITY ANALYSIS

All the identified natural compounds were analyzed for their blood-brain barrier permeability by using the online BBB prediction server- Cbligand. It is a free web tool to predict the BBB permeation of small molecules [428].

6.2.3 MOLECULAR DOCKING STUDIES

The structures of CDK5 (PDB ID 1UNL, at a resolution of 2.20 Å), and GSK-3B complexed with AMPPNP (PDB ID 1J1B, at a resolution of 1.80 Å), were retrieved from the protein data bank PDB. CDK5 and GSK3B respectively contained roscovitine (ROS) and phosphoaminophosphonic acid-adenylate ester (AMPPNP) as bounded ligands which served as control for comparing docking energies and ligand interactions. The ligand files (SDFs) were downloaded from PubChem database and converted to PDB files by using OpenBabelGUI. Study of receptor-ligand docking was conducted with Autodock vina [429] with a box size of 40 x 40 x 40. In order to obtain a clean protein structure, functional ligands, water molecules were removed from the protein structures. In this study, the active sites were predicted by using Biovia Drug discovery studio visualizer 2020.

6.2.4 MOLECULAR DYNAMICS SIMULATION

Dynamic studies were conducted on complex files with the best binding energy. A molecular dynamics simulation of a selected protein-ligand complex was performed with Gromacs-2019.4. The forcefield coordinates were obtained by downloading the ligand topology from the Prodrug server. A steepest descent algorithm was used for pre-processing the system using 1500 steps of vacuum minimization. A SPCE water model was used to solvate the complex structures in a cubic periodic box of 0.5 nm. Following this, the salt concentration of the complex systems was maintained at 0.15 M using a suitable number of Na+ and Cl- counterions. It was based on the results of a previously published paper that the system preparation took place. The final production run of each structure from the equilibration phase was conducted using an ensemble of NPT (Number of atoms in the system, pressure of the system and temperature of the system) simulations for 50 ns. An analysis of trajectory was conducted using the RMSD, RMSF, RG and H-Bond simulation packages in Gromacs.

6.2.5 ANALYSIS OF PHYSICOCHEMICAL PARAMETERS, ADME AND TOXICITY PROFILE PREDICTION

The bioavailability of a drug is influenced by different physicochemical properties like molecular size, lipophilicity, water solubility and permeability as determined by Lipinski's rule of five. Similarly, the prediction of ADME (absorption, distribution, metabolism, excretion) properties is necessary for drug development and prioritization. The prediction of various physicochemical parameters and ADME (absorption, distribution, metabolism, excretion) properties was made by the online tool SwissADME [325], and toxicity profiling was performed by the Pro-Tox server [431].

The workflow of all the methods is provided in **Figure 5.1**

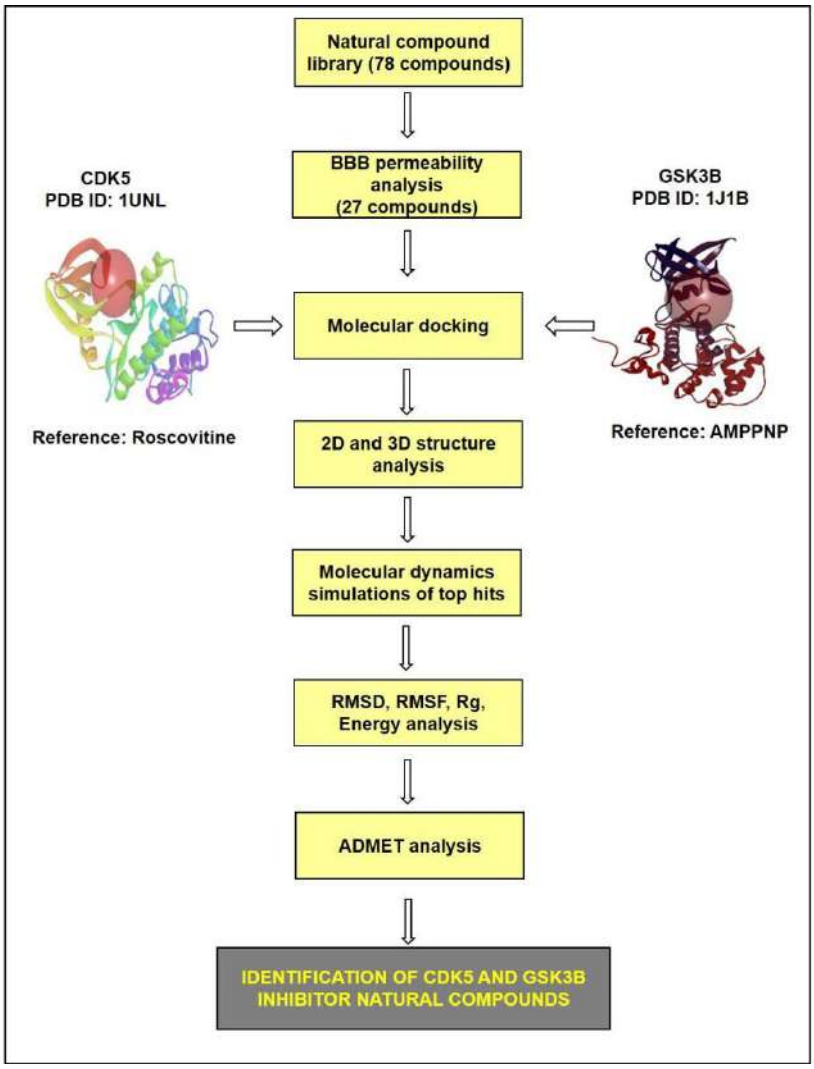


Figure 6.1: Flow chart of the methodology used in the study.

6.3 RESULTS

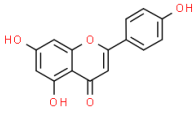
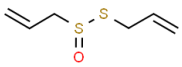
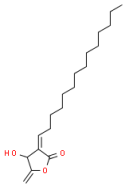
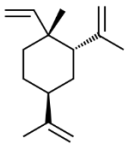
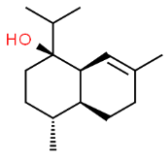
6.3.1 IDENTIFICARION OF NATURAL COMPOUNDS

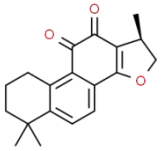
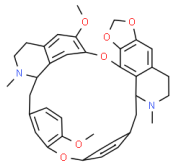
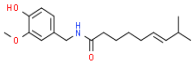
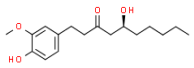
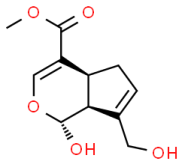
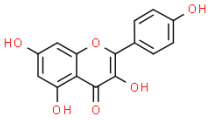
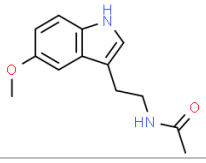
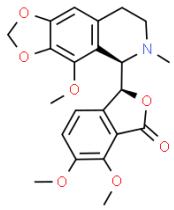
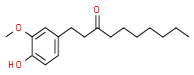
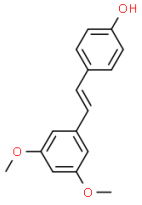
From the available literature studies, 78 natural compounds with anticancer properties were identified. The list of compounds is provided in **Annexure 9**. These compounds belong to different classes such as flavonoids, alkaloids, phenols and other classes.

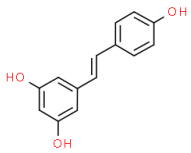
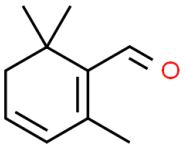
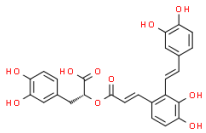
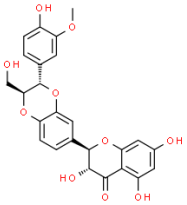
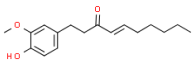
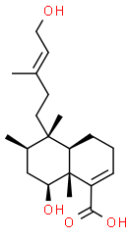
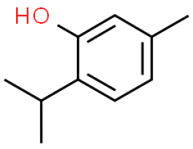
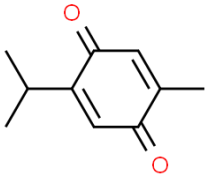
6.3.2 BBB PERMEABILITY ANALYSIS

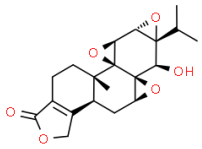
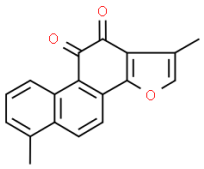
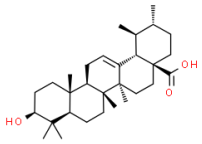
BBB permeability analysis found out of 78 natural compounds, 27 compounds were able to cross BBB and can be used as input for docking analysis. We selected a 0.02 value as the threshold and all the compounds with higher scores were considered as BBB penetrant drugs. The BBB scores of various compounds vary from 0.02 to 0.18, with ursolic acid showing the lowest score and allicin showing the highest score. The complete list of drugs with their BBB scores is provided in the **Table 6.1**.

Table 6.1: Summary of BBB permeable natural products with their respective BBB scores, associated class and their 2D structures

S.No.	Natural product	Class	Structure	BBB score
1	Apigenin	Flavonoid		0.022 (**BBB+**)
2	Allicin	Sulfoxide		0.18 **(BBB+)**
3	Borbonol	Nitro compound		0.057 **(BBB+)**
4	Beta-elemene	Terpene		0.089 **(BBB+)**
5	Chamomillol	Terpene		0.032 **(BBB+)**

6	Cryptotanshinone	Trepene		0.056 **(BBB+)**
7	Cepharanthine	Isoquinoline		0.076 **(BBB+)**
8	Capsaicin	Phenol		0.064 **(BBB+)**
9	Gingerol	Beta-hydroxy ketone		0.023 **(BBB+)**
10	Genipin	Beta-hydroxy ketone		0.022 **(BBB+)**
11	Kaempferol	Flavonoid		0.021 **(BBB+)**
12	Melatonin	Indole		0.101 **(BBB+)**
13	Noscapine	Isoquinoline		0.042 **(BBB+)**
14	Paradol	Phenol		0.058 **(BBB+)**
15	Pterostilbene	Stilbenoid		0.027 **(BBB+)**

16	Resveratrol	Phenol		0.041 **(BBB+)**
17	Sulforaphane	Isothiocynate		0.136 **(BBB+)**
18	Safranal	Phenol		0.036 **(BBB+)**
19	Salvianolic acid	Coumaric acid		0.031 **(BBB+)**
20	Silymarin	Flavonoid		0.033 **(BBB+)**
21	Shogaol	Phenol		0.069 **(BBB+)**
22	Salvicin	Beta-glucoside		0.053 **(BBB+)**
23	Thymol	Phenol		0.032 **(BBB+)**
24	Thymoquinone	Quinone		0.023 **(BBB+)**

25	Triptolide	Terpene		0.038 **(BBB+)**
26	Tanshinone	Terpene		0.063 **(BBB+)**
27	Ursolic acid	Terpene		0.020 **(BBB+)**

6.3.3 BINDING MECHANISM OF CDK5 AND GSK3B INHIBITOR COMPOUNDS

Understanding of physical interactions of protein and ligands is an essential step in computational drug designing. To understand the binding affinities of query ligands to the proteins, we first docked the reference drug ROS to CDK5 and AMPPNP to GSK3B and then identified the interacting residues. The substrate binding site of CDK5 and GSK3B was analyzed and presented in **Figure 6.2 (a) and Figure 6.3 (a),** respectively. We found that ROS interacted with CDK5 with docking energy -8.7 Kcal/mol. The drug positioned itself in the hydrophobic pocket of CDK5 consisting of Ile10, Gly11, Glu12, Gly13, Val18, Ala31, Lys33, Val64, Phe80, Phe82, Asp84, Gln85, Asp86, Lys89, Gln130, Leu133, Ala143, Asn144 residues where there is one H-bond formed with Cys83 residue with a distance of 2.81Å **[Figure 6.2 (b) and (c)].**

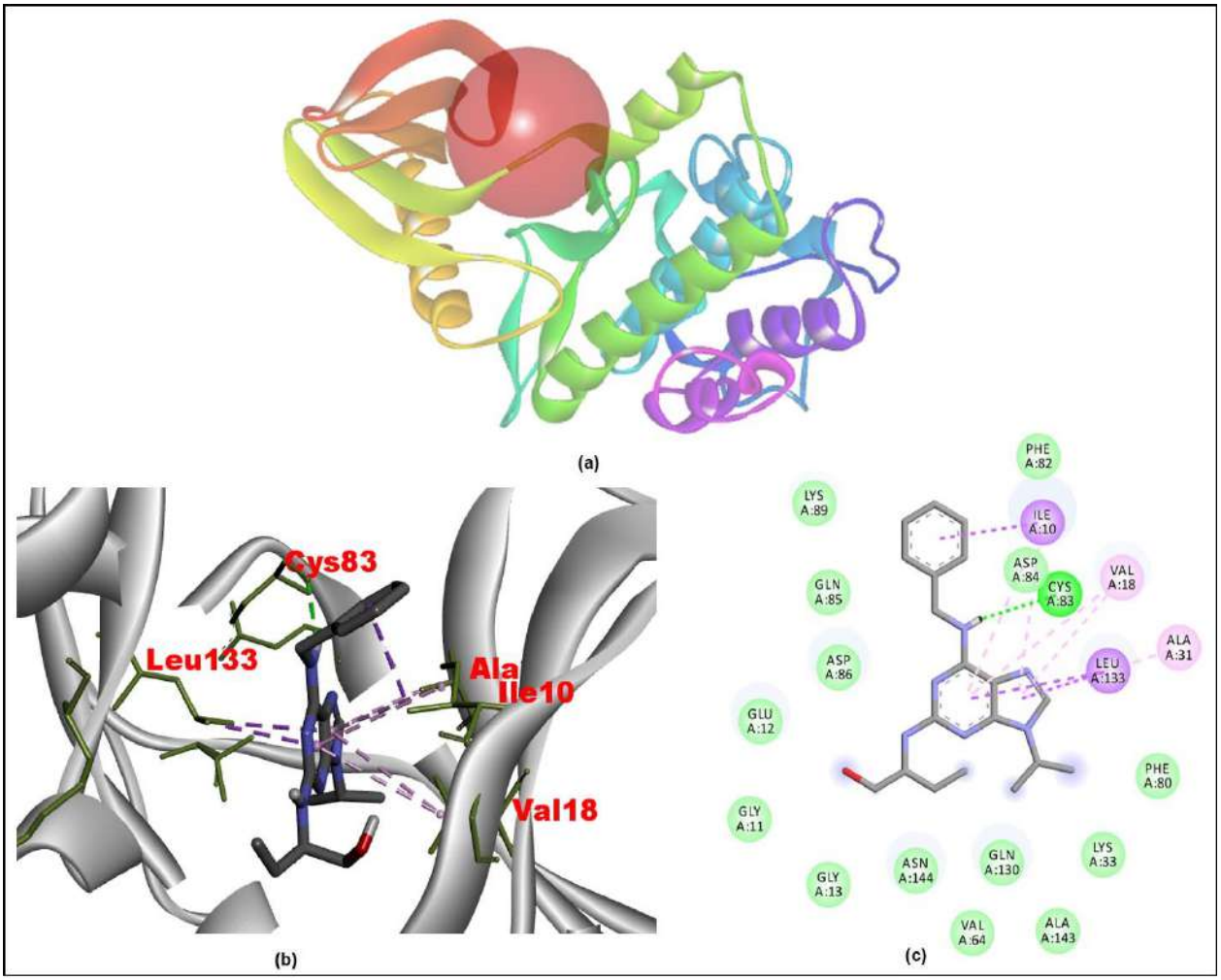


Figure 6.2: (a) Structure of CDK5 chain A is shown where the red circle represents the substrate binding site. (b) 3D structure of the binding mode of roscovitine with CDK5 (c) 2D structure of the binding pattern of the reference drug roscovitine with CDK5. Dark green lines interactions represent H-bonds, light green represents Vander Waals, pink represents alkyl and pi-alkyl, and blue represent pi-sigma interactions.

Likewise, AMMPNP interacted with GSK3B with docking energy -8.1Kcal/mol. The adenine group of AMPPNP forms two H-bonds with residues Asp133 and Val135, the ribose ring forms a H-bond with Ile62 and two oxygen atoms of the terminal phosphate moiety form three H-bonds with residues Ser66, Phe67, and Gly68. Besides, hydrophobic interactions were formed between adenine group of AMPPNP with residues Val70, Ala83, and Leu188 **[Figure 6.3 (b) and (c)].**

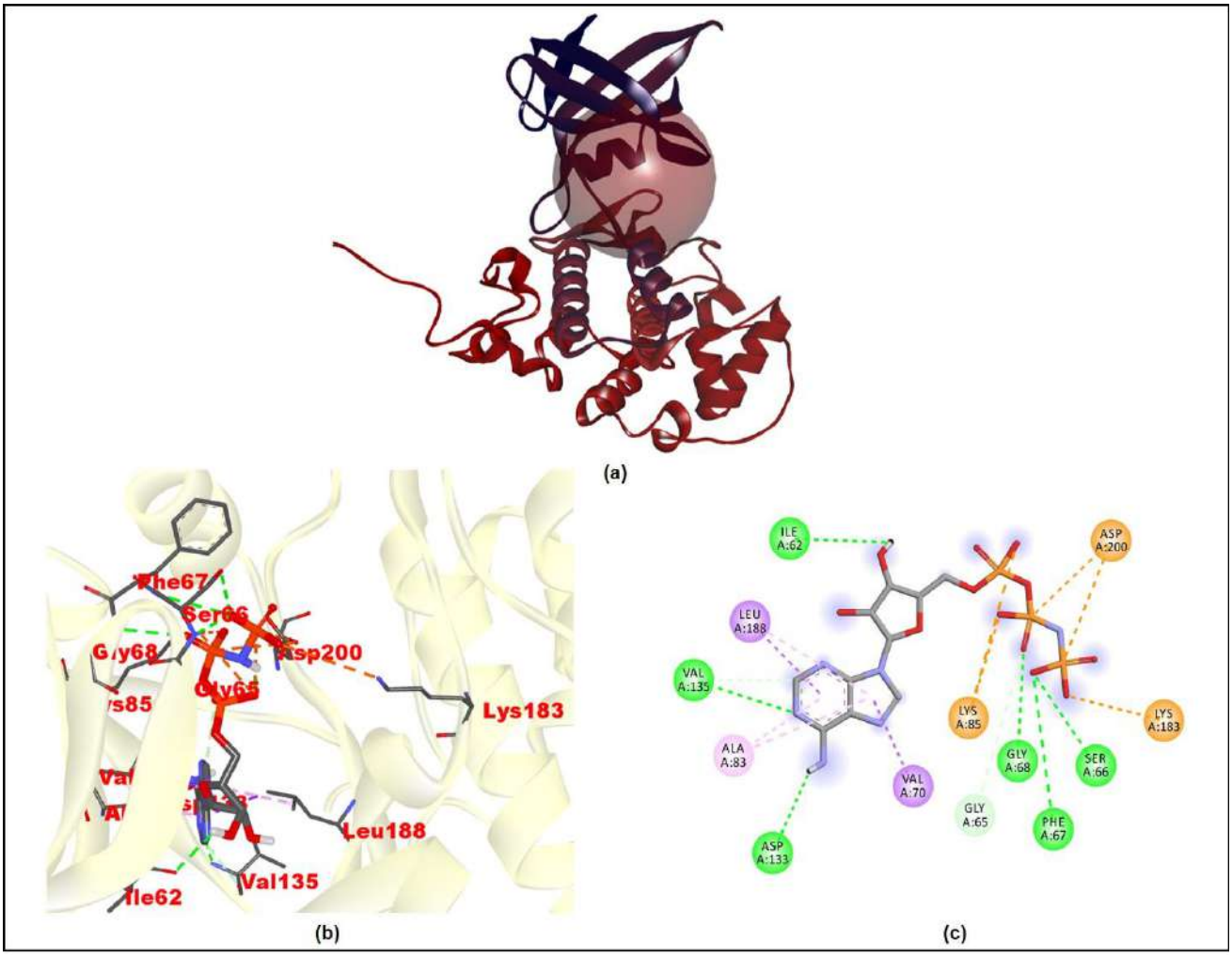


Figure 6.3: (a) Structure of GSK3B chain A is shown where the red circle represents the substrate binding site. (b) 3D structure of the binding mode of AMPPNP with GSK3B (c) 2D structure of the binding pattern of the reference compound AMPPNP with GSK3B. Dark green lines interactions represent H-bonds, light green represents Vander Waals, pink represents alkyl and pi-alkyl, blue represents pi-sigma interactions and orange represents salt bridge interactions

A total of 27 BBB permeable compounds were selected for docking analysis. For CDK5, out of 27 compounds, 11 compounds were showing interactions with the active site residues while for GSK3B, 8 compounds were showing interactions. The docking analysis of all the selected natural compounds with CDK5 and GSK3B with docking energies and interacting residues are represented in **Table 6.2** and **Table 6.3**, respectively.

Table 6.2: Docking details of the compounds against CDK5 protein along with the reference drug including docking energies, H-bonds and other interactions.

Compound	Docking energy (Kcal/mol)	H-bond with distance	Non polar interactions
Roscovitine	-8.7	**Cys83 (2.81Å)**	Val18, Ala31 (pi-alkyl), Ile10, Leu133 (pi-sigma), Gly11, Glu12, Gly13, Lys33, Val64, Phe80, Phe82, Asp84, Gln85, Asp86, Lys89, Gln130, Ala143, Asn144
Salvianolic acid	-9.3	Glu12 (2.06 Å) Glu81 (2.36 Å) Asp86 (3.32 Å) Asn144 (2.94 Å)	Val18, Ala31 (pi-alkyl), Phe80 (pi-pi), Ile10 (pi-sigma), Gly13, Thr14, Lys33, Val64, Phe82, Cys83, Asp84, Gln85, Lys89, Lys128, Gln130, Asn131 (Van der Waals)
Silymarin	-8.7	Glu81 (2.46 Å)	Lys88 (alkyl), Gly11 (C-H), Val18, Ala31, Val64, Lys88, Lys89 (pi-alkyl), Asp86 (pi-anion), Ile10, Leu133 (pi-sigma), Glu12, Glu51, Phe82, Cys83, Asp92, Ala143, Asn144 (Van der Waals)
Apigenin	-8.7	Glu81 (2.61 Å) **Cys83** (2.91 Å)	Val18, Ala31 (pi-alkyl), Ile10, Leu133 (pi-sigma), Lys33, Val64, Phe80, Phe82, Asp84, Gln85, Asp86, Lys89, Asn144 (Van der Waals)
Kaempferol	-7.8	Lys33 (3.35Å)	Ile10, Ala31 (pi-alkyl), Asp86 (pi-anion), Val18, Leu133 (pi-sigma), Gly11, Glu12, Gly13, Thr14, Val64, Glu81, Phe80, Phe82,Gln130, Asn144 (Van der Waals)
Chamomillol	-7.7	Asn144	Val18, Ala31, Leu133 (alkyl), Ile10, Glu12, Gly13, Val64, Phe80, Cys83, Asp86, Ala143 (Van der Waals)
Resveratrol	-7.5	Glu81 (2.13 Å) Asp84 (3.08 Å)	Val18, Ala31 (pi-alkyl), Ile10, Leu133 (pi-sigma), Phe80 (pi-pi), Val64, Cys83, Gln85, Asp86, Lys89, Asn144 (Van der Waals)
Noscapine	-7.4	Asp86 (3.24 Å)	Ala31, Phe82, Cys83 (alkyl), Val18 (pi-alkyl), Ile10, Leu133 (pi-sigma), Gly11, Glu12, Gly13, Asp84, Gln85, Gln130, Asn144 (Van der Waals)
Gingerol	-7.1	Asn144 (3.08Å)	Val18, Ala31, Lys33, (alkyl), Lys89, Leu133 (pi-alkyl), Val64, Phe82, Cys83, Asp84, Gln85, Asp86, Ala143 (Van der Waals)
Paradol	-7.1	**Cys83** (2.00 Å) Asp86 (3.03 Å) Asn144 (2.13 Å)	Val18, Ala31, Lys33, Val64, Lys89, Ala143 (Alkyl), Phe80, Ile10 (pi-alkyl), Leu133 (pi-sigma), Glu81, Phe82, Asp84, Gln85 (Van der Waals)
Thymoquinone	-7.1	**Cys83** (3.01 Å)	Ile10, Ala31 (Pi-alkyl), Val18, Phe80, Leu133 (Pi-sigma), Lys33, Val64, Phe82, Ala143, Asn144 (Vander Waals)
Genipin	-6.9	Glu81 (2.04Å) Asn144 (3.09Å)	Ile10, Val18, Ala31, Leu133 (alkyl), Gly13 (C-H), Lys33, Val64, Phe80, Phe82, Cys83 (Van der Waals)

*** H-bonds are highlighted in bold**

Table 6.3: Docking details of the compounds against GSK3B protein along with the reference drug including docking energies, H-bonds and other interactions.

Compound	Docking energy (Kcal/mol)	H-bond with distance	Non polar interactions
AMPPNP	-8.1	Ile62 Ser66 Gly68 Phe67 Asp133 Val135	Gly65 (C-H), Ala83 (pi-alkyl), Val70, Leu188 (pi-sigma), Lys85, Lys183, Asp200 (Salt bridge)
Salvianolic acid	-8.6	Lys85 Thr138 Arg141	Val70, Ala83 (pi-alkyl), Leu188 (pi-sigma), Ile62, Gly63, Asn64, Gly65, Phe67, Val110, Leu132, Tyr134, Asp133, Tyr140, Gln185, Cys199, Asp200 (Vander Waals)
Apigenin	-8.1	Lys85 **Val135**	Tyr134 (C-H), Val70, Ala83, Leu188, Cys199 (pi-alkyl), Ile62 (pi-sigma)
Kaempferol	-8.1	**Asp133** **Val135** Asp200	Ile62, Val70, Ala83, Leu188, Cys199 (pi-alkyl), Lys85, Val110, Leu132, Tyr134, Arg141, Asn185, Asn186 (Vander Waals)
Noscapine	-7.7	Lys85	Ile62, Asn64, Cys199 (C-H), Tyr140 (alkyl), Val70, Leu188 (pi-alkyl), Gly63, Val110, Leu132, Thr138, Arg141, Lys183, Gln185, Asn186, Asp200, Ph201
Pterostilbene	-7.0	Arg141	Asp133, Tyr134 (C-H), Ala83, Val135, Leu188 (alkyl), Val70, Lys85, Cys199 (pi-alkyl), Ile62 (pi-sigma), Gly63, Asn64, Asp200 (Vander Waals)
Melatonin	-6.8	**Ile62** Lys85 Arg141	Cys199 (C-H), Val70, Ala83, Leu188 (pi-alkyl), Gly63, Val110, Leu132, Tyr134, Val135, Thr138, Asp200 (Vander Waals)
Shogaol	-6.6	Lys85 **Val135**	Ile62 (C-H), Val70 (alkyl), Ala83, Cys199 (pi-alkyl), Leu188 (pi-sigma), Asn64, Gly65, Phe67, Gly68, Val110, Leu132, Asp133, Tyr134, Arg141, Asp200 (Vander Waals)
Paradol	-6.1	Lys85 **Val135**	Cys199 (C-H), Ile62, Val70, Leu132 (alkyl), Gly63, Ala83, Glu97, Met101, Val110, Thr138, Arg141, Asp133, Tyr134, Thr138, Leu188, Asp200, Phe201 (Vander Waals)

*** H-bonds are highlighted in bold**

For CDK5, the highest docking energy was observed for salvianolic acid (SAL) (-9.3 Kcal/mol) and lowest energy was for genipin (-6.9Kcal/mol). We found that only three compounds- SAL (-9.3 Kcal/mol), silymarin (SLY) (-8.7 Kcal/mol), and apigenin (API) (-8.7 Kcal/mol), have shown better docking energies as compared to the reference drug. The binding patterns of all these compounds are presented in **Figure 6.4**. H-bond interaction

analysis had shown that API formed two H-bonds with CDK5 while SAL and SLY formed four and two H-bonds, respectively. We have seen that Ile10, Val18, Ala31, Val64, Phe80, Glu81, Phe82, Cys83, Lys89, and Asn144 were the common interacting residues among all the three compounds and are also presented in the experimental structure in CDK5-ROS interaction.

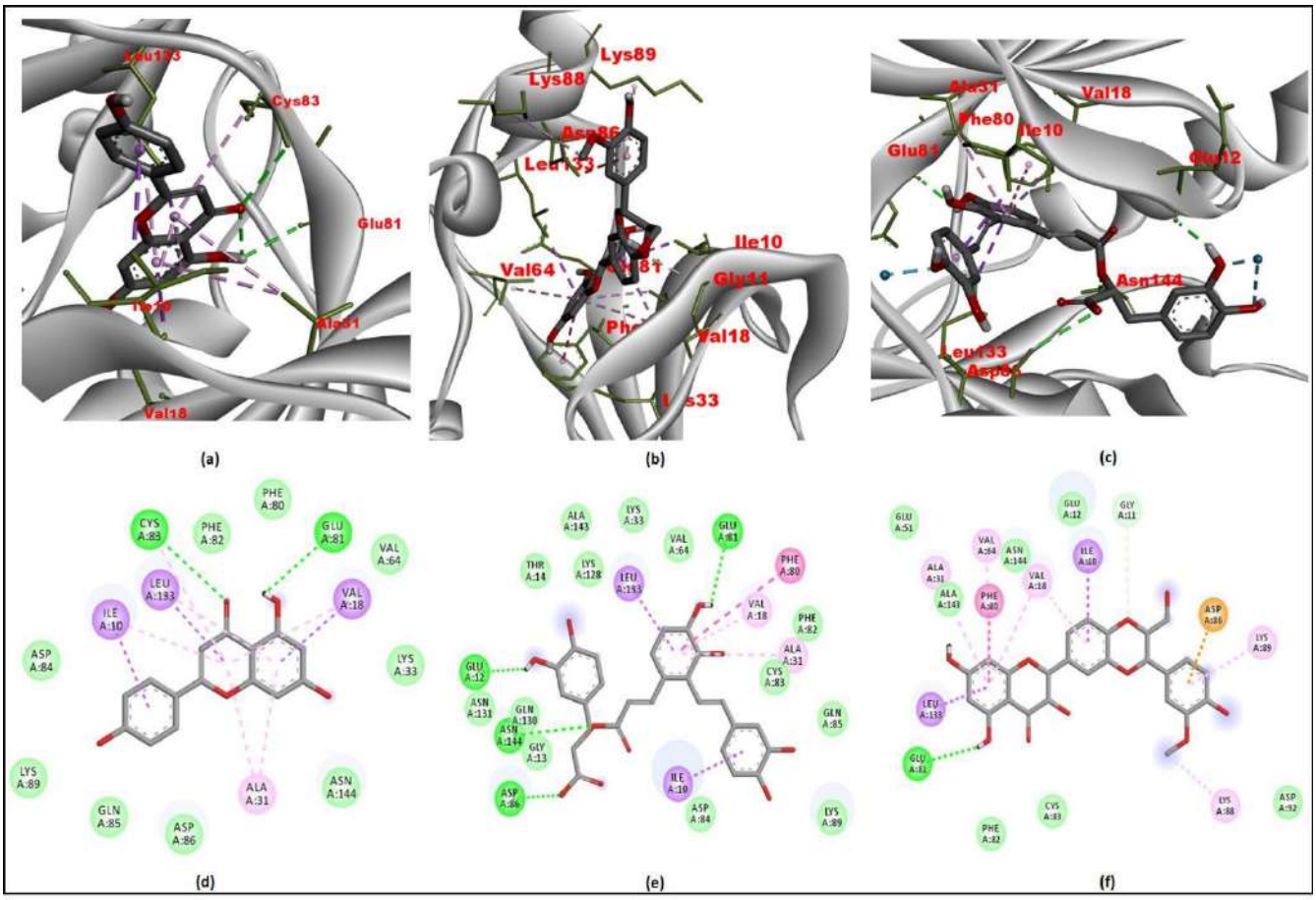


Figure 6.4: (a) and (d) 3D and 2D structures of the binding pattern of apigenin with CDK5 (b) and (e) 3D and 2D structures of the binding pattern of salvianolic acid with CDK5 (c) and (f)) 3D and 2D structures of the binding pattern of silymarin with CDK5. Dark green lines interactions represent H-bonds, light green represents Vander Waals, pink represents alkyl and pi-alkyl, and blue represents pi-sigma interactions. Dark green lines interactions represent H-bonds, light green represents Vander Waals, pink represents alkyl and pi-alkyl, dark pink represents pi-pi interactions, blue represents pi-sigma interactions and orange represents anionic interactions.

For GSK3B, out of eight docked compounds, SAL (-8.6 Kcal/mol), API (-8.1 Kcal/mol), and kaempferol (KEM) (-8.1 Kcal/mol), were showing better docking energies as compared to the reference compound. The binding pattern of all these compounds are

shown in **Figure 6.5**. The H-bond interaction analysis revealed that both API and SLY formed two H-bonds with GSK3B while SAL formed three H-bonds. Additionally, Ile62, Val70, Ala83, Tyr134, and Leu188 were the common residues among the three compounds that were found to be interacting with GSK3B.

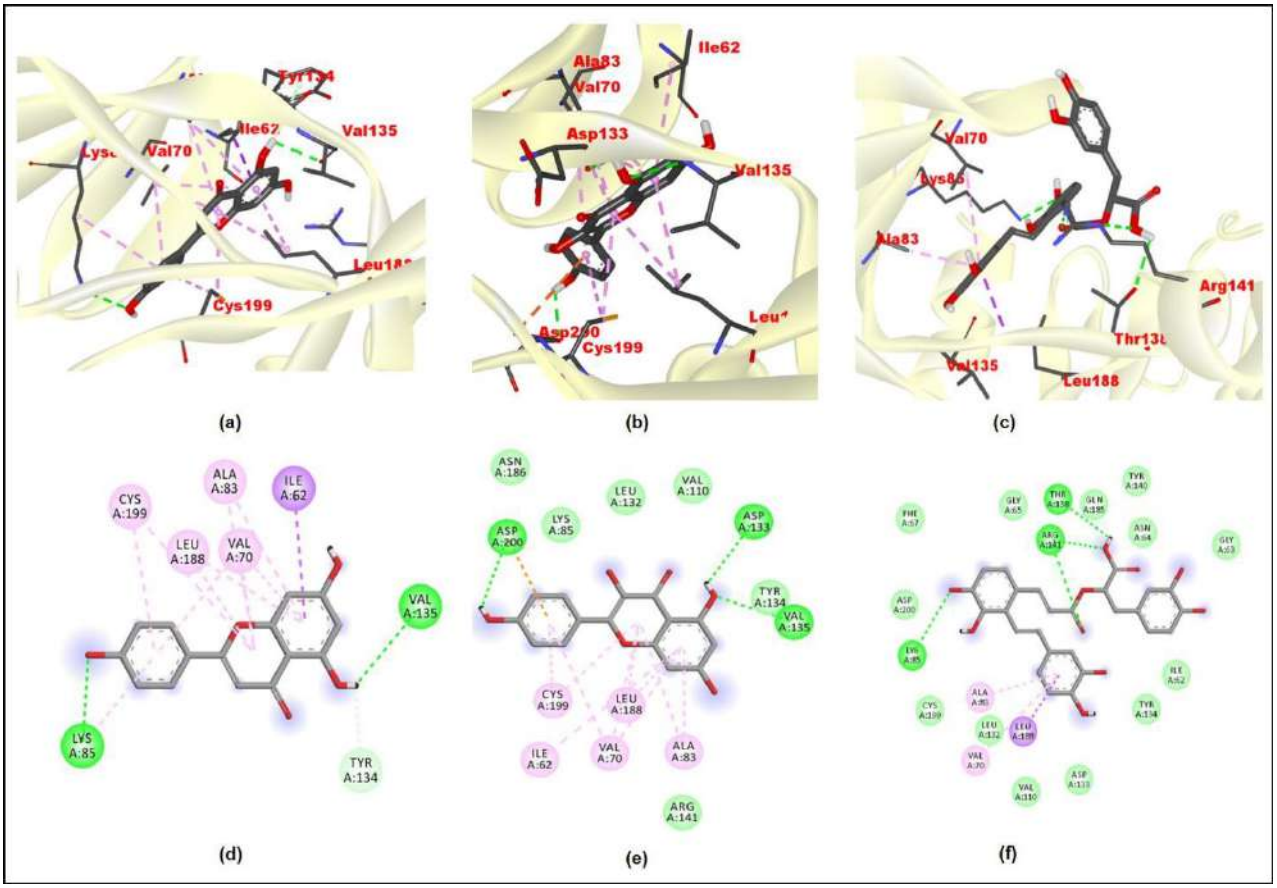
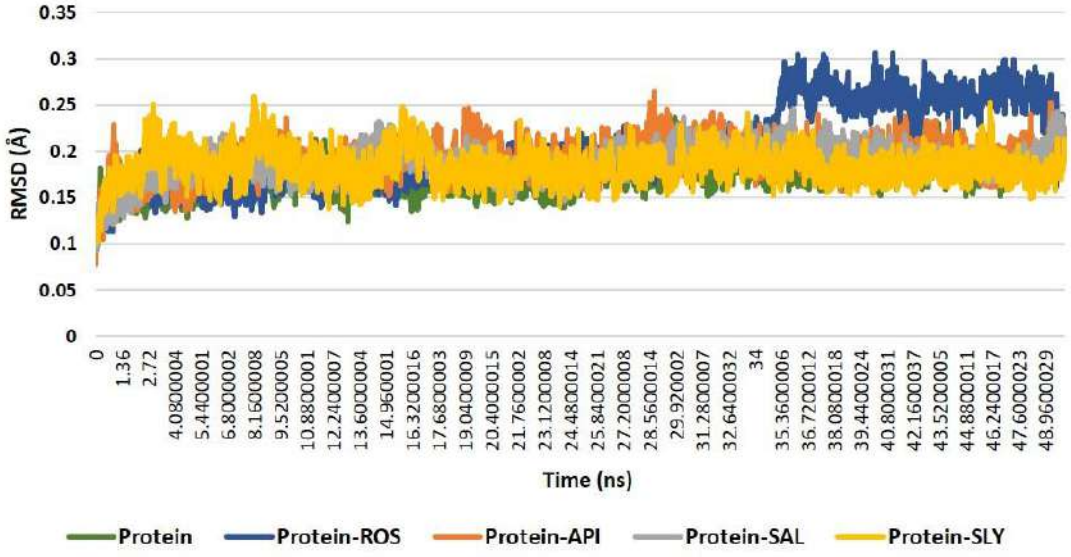


Figure 6.5: (a) and (d) 3D and 2D structures of the binding pattern of apigenin with GSK3B (b) and (e) 3D and 2D structures of the binding pattern of kamepferol with GSK3B (c) and (f)) 3D and 2D structures of the binding pattern of salvianolic acid with GSK3B. Dark green lines interactions represent H-bonds, light green represents Vander Waals, pink represents alkyl and pi-alkyl, and blue represents pi-sigma interactions. Dark green lines interactions represent H-bonds, light green represents Vander Waals, pink represents alkyl and pi-alkyl, dark pink represents pi-pi interactions, and blue represents pi-sigma interactions.

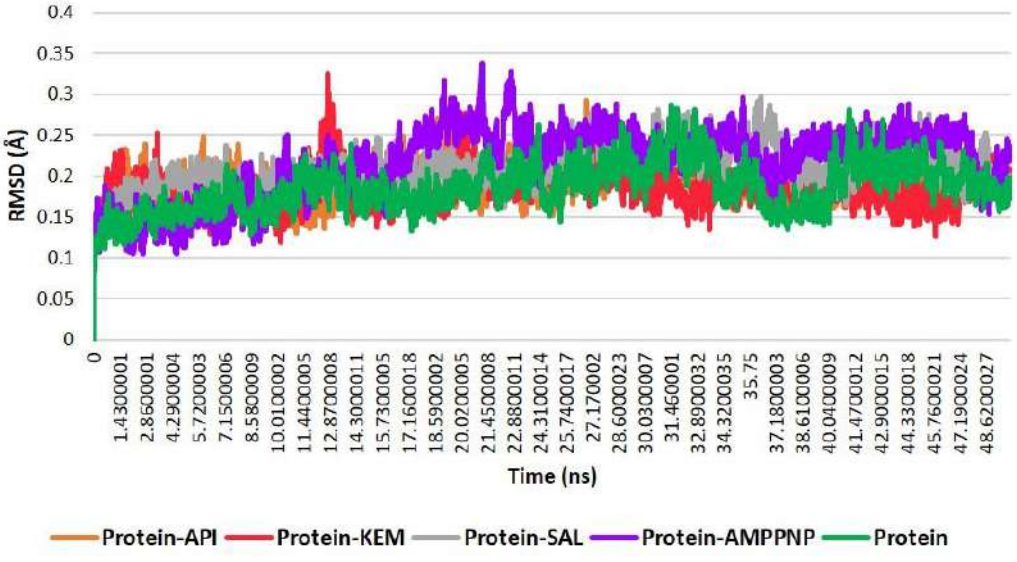
6.3.4 STRUCTURAL DEVIATION, FLEXIBILITY, COMPACTNESS AND BINDING FREE ENERGY ANALYSIS

To understand the binding pattern and molecular interactions of the selected natural compounds with CDK5 and GSK3B, molecular dynamics simulation was performed for 50ns time period. As shown in **Figure 6.6 (A) and (B),** the RMSD analysis of protein

backbone atoms, reference drugs and natural compounds are compared. We found that all the systems remained in steady state and did not deviate more than 0.3 Å. Further, all three compounds had less deviation compared to the reference drug and there were comparable fluctuations for the three compounds.



(A) RMSD analysis for CDK5 protein

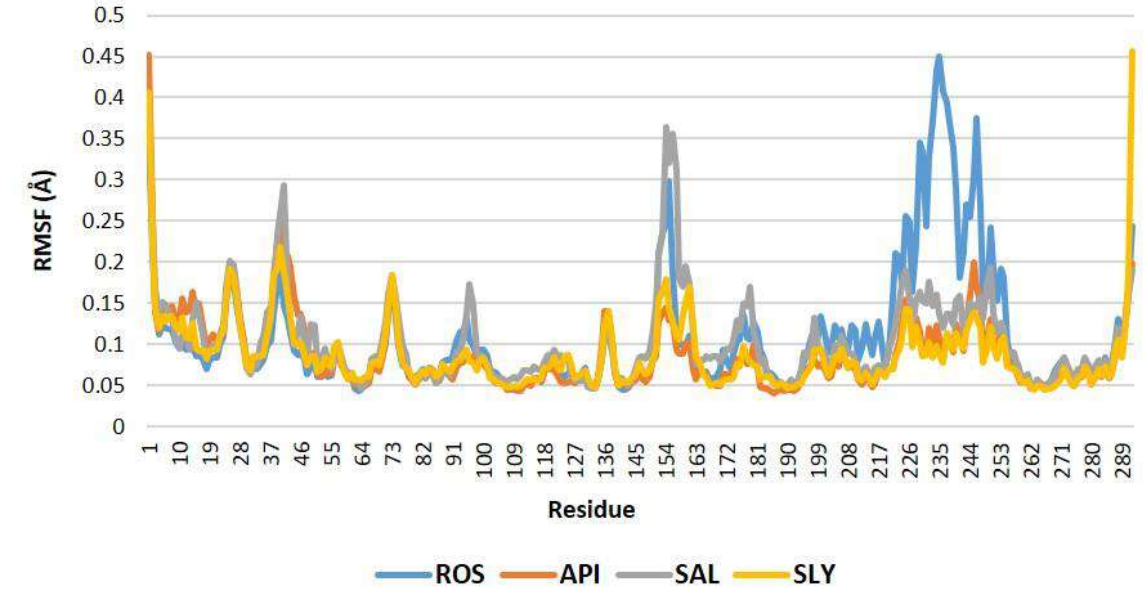


(B) RMSD analysis for GSK3B protein

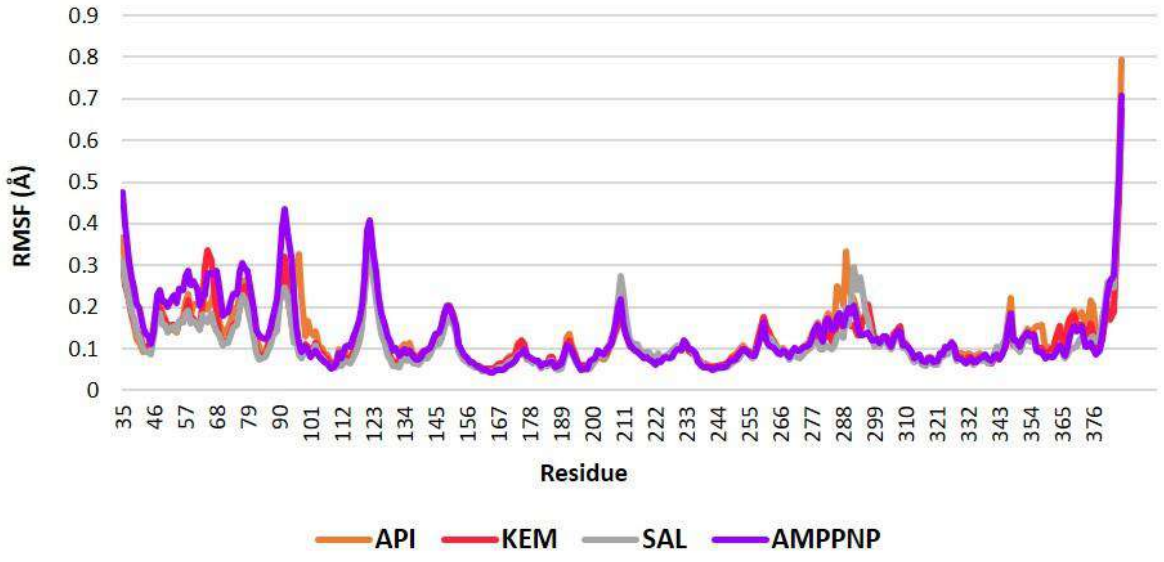
Figure 6.6: Root mean square deviation analysis of the reference compound and the test compounds with (A) CDK5 and (B) GSK3B. The threshold RMSD was taken as 0.3Å and the fluctuations within this limit were considered as acceptable.

To understand the residue flexibility of all the systems, RMSF analysis was carried out for the complete simulation period. From **Figure 6.67(A),** it was clear that in case of CDK5, all the systems were fluctuating differently, with CDK5/API had the lowest fluctuation. We found that for CDK5/ROS complex, residues 220-250, for CDK5/SAL complex, residues 150-158, and for CDK5/SLY, residues 285-290, were showing variations. Similarly, the residue flexibility for the bound GSK3B was shown in **Figure 6.7 (B).** For GSK3B/AMPPNP complex, residues 346-353, for GSK3B/API complex, residues 90-98, for GSK3B/KEM residues 57-60 and residues 85-92, and for GSK3B/SAL, residues 345-353, were considered as the flexible residues. For compactness analysis, we performed Rg analysis of all the systems.

To understand the conformational changes of the protein complexes, Rg analysis has been performed. As shown in **Figure 6.8 (A),** CDK5/ROS and CDK5/API have shown less fluctuation while CDK5/SAL and CDK5/SLY have higher values of Rg, indicative of slightly labile nature of the systems. As evident from **Figure 6.8 (B),** the Rg values for all the complexes were consistent with GS3B/AMPPNP.

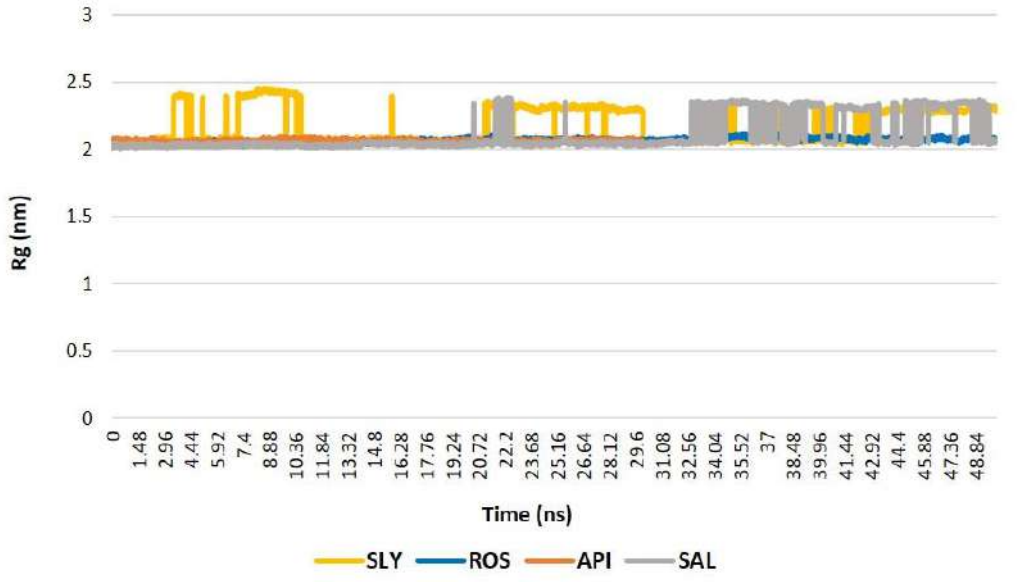


(A) RMSF analysis for CDK5 protein

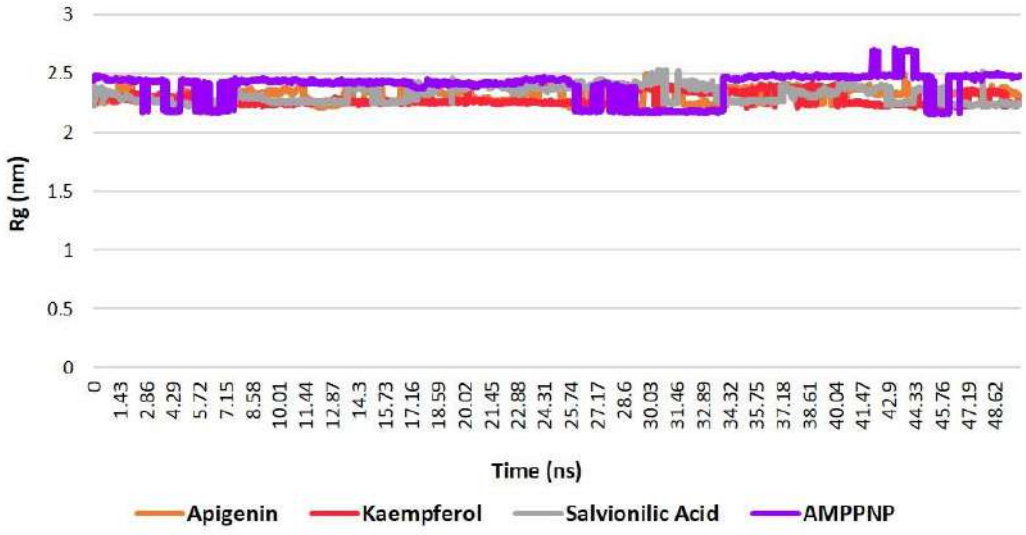


(B) RMSF analysis for GSK3B protein

Figure 6.7: Root mean square fluctuation (RMSF) analysis of the reference compound and the test compounds with (A) CDK5 and (B) GSK3B. The fluctuations are interpreted by observing the peaks of the graphs



(A) Rg analysis for CDK5 protein



6. Rg analysis for GSK3B protein

Figure 6.8: Radius of gyration (Rg) analysis of the reference compound and the test compounds with (A) CDK5 and (B) GSK3B. The lower values represent protein stability, while the higher values represent protein flexibility.

To understand the binding mechanism of all the compounds, we have done interaction energy analysis. The binding affinity of various inhibitors to CDK5 protein was done by

comparing the Coulomb's energy of various inhibitors with ROS as presented in **Figure 6.9 (a)**. We found that the average Coulomb's energy of both API and SAL were higher than ROS while for SLY the energy value was lower. From **Figure 6.9 (b)**, we found that only KEM had higher Coulomb's energy as compared to the reference drug.

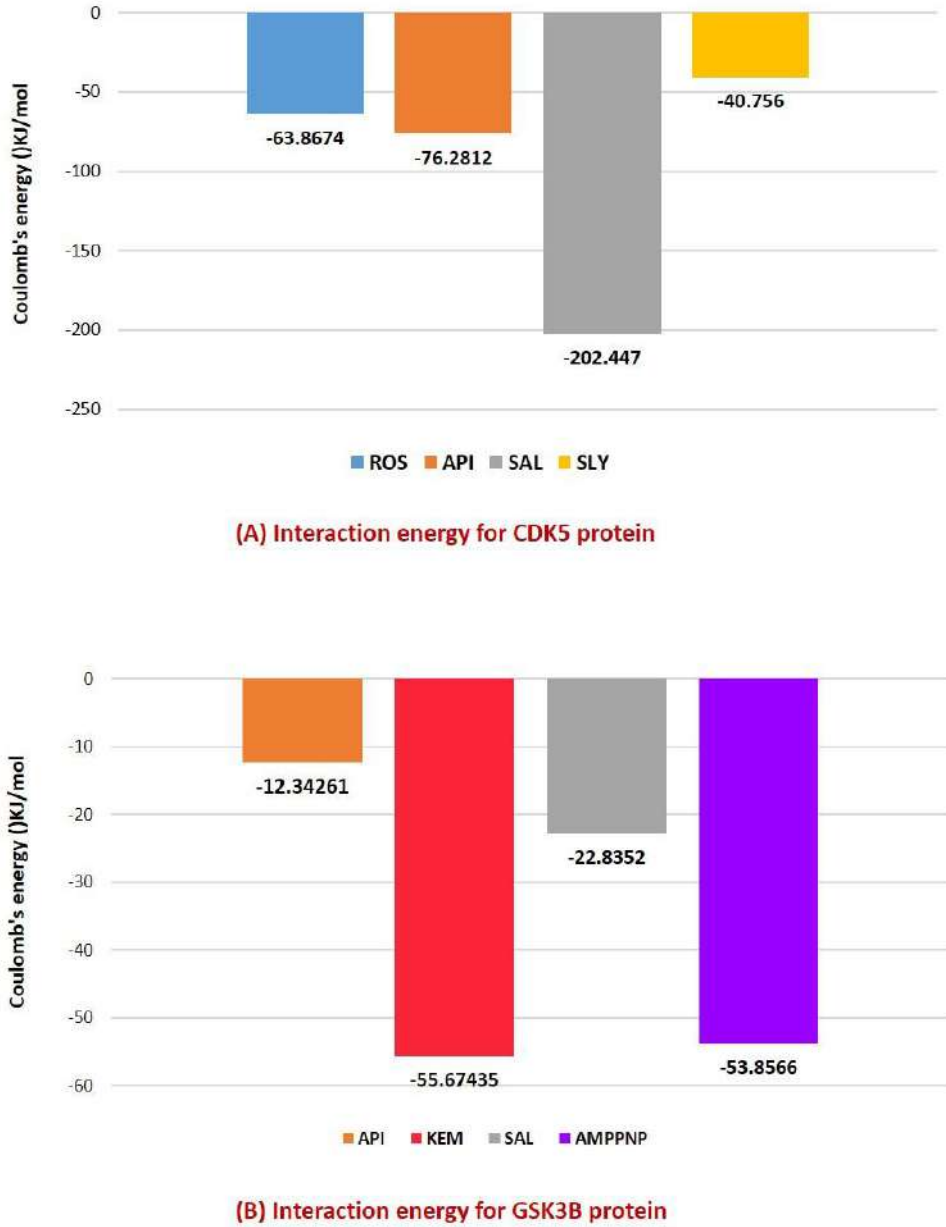


Figure 6.9: Binding free energies (Coulomb's energy) for the compounds with (A) CDK5 and (B) GSK3B. The higher interaction energy represents the higher stability of the protein-inhibitor complex.

6.3.5. ASSESSMENT OF PHARMACOKINETIC PROPERTIES AND TOXICITY PROFILE

The prediction of physiochemical parameters and determination of ADMET properties are considered as crucial factors in drug designing process. The important physicochemical features including molecular weight (MW), number of hydrogen bond donors (HBD) and acceptors (HBA), number of rotatable bonds, and topological polar surface area (TPSA), and various ADMET descriptors were estimated for all the 27 compounds **(Table 6.3).** In keeping with the rule of five all the compounds were in accordance with the set parameters and no violation was found. Likewise, the ADME parameters including water solubility (log S), and octanol/water partition coefficient (log P), were found to be suitable. The toxicity analysis has shown that two compounds- capsaicin, and triptolide were toxic while other compounds were related to moderately toxic and non-toxic categories. The various toxicity parameters such as cytotoxicity, carcinogenicity, hepatotoxicity, mutagenicity, immunogenicity and LD50 values are presented in **Annexure 10.**

Table 6.4: ADMET properties of the 27 natural compounds

Natural product	MW	RB	HBA	HBD	TPSA	Log P	Log S	Lipinski's rule	Toxicity
Apigenin	270	1	5	3	90.9	2.58	-3.94	Yes	Non-toxic
Allicin	162.27	5	1	0	61.58	1.95	-1.34	Yes	Moderate
Borbonol	308.46	12	3	1	46.53	5.05	-5.2	Yes	Non-toxic
Beta-elemene	204.35	3	0	0	0	4.75	-4.76	Yes	Non-toxic
Chamomillol	222.37	1	1	1	20.23	3.78	-3.48	Yes	Moderate
Cryptotanshinone	296.36	0	3	0	43.37	3.44	-4.27	Yes	Non-toxic
Cepharanthine	606.71	2	8	0	61.86	4.98	-7.98	Yes	Moderate
Capsaicin	305.41	10	3	2	58.56	4.18	-3.53	Yes	Toxic
Gingerol	294.39	10	4	2	66.76	3.48	-3.23	Yes	Moderate
Genipin	226.23	3	5	2	75.99	-0.05	-0.57	Yes	Moderate

Kaempferol	286.24	1	6	4	111.13	2.82	-3.31	Yes	Non-toxic
Melatonin	232.28	5	2	2	54.12	1.98	-2.34	Yes	Moderate
Noscapine	413.42	4	8	0	75.69	3.59	-4.14	Yes	Moderate
Paradol	278.39	10	3	1	46.53	4.26	-3.72	Yes	Non-toxic
Pterostilbene	256.3	4	3	1	38.69	3.58	-4.01	Yes	Moderate
Resveratrol	228.24	2	3	3	60.69	2.97	-3.62	Yes	Moderate
Sulforaphane	177.29	5	2	0	80.73	2.11	-1.5	Yes	Moderate
Safranal	150.22	1	1	0	17.07	6	-2.05	Yes	Moderate
Salvianolic acid	492.43	8	10	6	177.89	1.63	-5.36	Yes	Non-toxic
Silymarin	482.44	4	10	5	155.14	2.36	-4.14	Yes	Moderate
Shogaol	276.37	9	3	1	46.53	4.04	-3.7	Yes	Moderate
Salvicin	336.47	5	4	3	77.76	3.54	-4.1	Yes	Non-toxic
Thymol	150.22	1	1	1	48.01	2.82	-3.19	Yes	Moderate
Thymoquinone	164.2	1	2	0	34.14	1.67	-2.18	Yes	Non-toxic
Triptolide	360.4	1	6	1	84.12	1.1	-2.15	Yes	Toxic
Tanshinone	276.29	0	3	0	47.28	4.1	-4.41	Yes	Moderate
Ursolic acid	456.7	1	3	2	57.53	7.09	-7.23	Yes	Moderate

Abbreviations: MW: molecular weight; RB: rotatable bond; HBA: H-bond acceptor; HBD: H-bond donor; TPSA: Total polar surface area

6.4. DISCUSSION

In this *in silico* study, we attempted to identify natural compounds as inhibitors of CDK5 and GSK3B enzymes which can be simultaneously used for the treatment of AD and PD. A plethora of studies have considered CDK5 and GSK3B as attractive targets for various neurological disorders that involve defective learning and memory functions [32]. Although a number of known CDK5 and GSK3B inhibitors are available and are tested in AD and PD but none of them have shown clinical success due to poor availability and low specificity. The current study aimed to identify some natural compounds as CDK5 and GSK3B inhibitors for the treatment of AD and PD. We developed a computational pipeline to screen natural compounds by

molecular docking and simulation studies. We used ROS and AMPPN as the reference drugs for CDK5 and GSK3B, respectively, as they have been known to cross BBB and shown neuroprotective functions and alleviation of neuronal death in various brain diseases.

The binding patterns of the reference drugs are identified from the literature studies. The substrate binding site of CDK5 comprised of a Gly-rich loop, an activation loop and the hinge region. A deeper analysis suggested that Lys33, Phe80, Glu81, Cys83, and Asn144 are the key residues regulating ATP binding and all CDK5 inhibitors occupy the ATP-binding site of the protein. It has been reported that ROS strongly binds to CDK5 through intermolecular H-bonds involving residues Cys83, Asp86 and Gln130. The interactions of all the identified natural compounds with CDK5 was analyzed by applying molecular docking approach. We identified API, SAL and SLY as potent compounds with good docking energies and significant interactions when compared to the reference drug. We observed that API interacted with CDK5 by forming two H-bonds and four hydrophobic interactions. A detailed mechanistic analysis revealed that both carbonyl and hydroxyl oxygens were involved in H-bonding while benzene and pyran rings were majorly involved in hydrophobic interactions such as pi-alkyl and pi-sigma interactions. Likewise, in SAL, three hydroxyl oxygens and one carbonyl oxygen were involved in H-bonding. The compound had five hydrophobic interactions where phenol ring had the major contribution. For SLY, one H-bond and ten different hydrophobic interactions were obtained. We found that one hydroxyl oxygen of was interacting with Glu81.

As observed in the binding patterns of AMPPNP with GSK3B, H-bonds interactions with Asp133, Val135, and Glu185, and hydrophobic interactions with Ile62, Val70, Ala83, Val110, Leu132, Tyr134 and Leu188 residues were considered important for binding. We identified that three compounds API, KEM, and SAL were having good docking energies and interactions

when compared to GSK3B. We found that H-bonds played a significant role in binding for all the three compounds with API forming two H-bonds and KEM and SAL forming three H-bonds. We observed that all three rings in API participate in binding interactions where one hydroxyl group of benzene ring and the hydroxyl group of the phenyl ring formed H-bonds. We found that in KEM, rings A and C majorly contribute to hydrophobic interactions while hydroxyl group at position 5 in ring A is H-bonded with residues Asp133 and Val135. Likewise, in SAL, two hydroxyl oxygens and one carbonyl oxygen were involved in H-bonding while dihydroxy phenyl ring majorly contributed to hydrophobic interactions.

To further validate our discovery, 50ns simulations were carried out on the selected docked compounds along with protein and reference drug. The RMSD analysis of all the systems revealed that the reference drug has shown higher amplitude than candidate inhibitor compounds. We presume that the candidate compounds may slightly be more stable than the reference drug. The RMSF analysis indicated that all the residues were fluctuating less over the simulation time. The compactness analysis revealed that all the three compounds remained stable over the simulation time when compared to the reference drug. Further, for CDK5 protein, API was found to be more stable with comparable values of gyration with the reference drug. The binding free energy analysis confirmed the stable interactions of candidate inhibitor drugs with CDK5 where SAL was having higher energy value. For GSK3B protein, only one compound KEM was having higher interaction energy than the reference compound. Based on these observations, we identified SAL as a better binding partner with CDK5 and KEM with GSK3B.

SAL is the phenolic acid isolated from the roots of *Salvia miltiorrhiza* (Danshen) and reported in literature with antioxidant, anti-inflammatory and anti-apoptotic properties. Some studies

have also highlighted the potential of SAL in treating AD as the compound is known to attenuate Aβ-induced neurotoxicity [445]. In PD, the compound is reported to overcome MPTP-induced neurotoxicity by inhibiting oxidative stress and mitochondrial dysfunction [446]. The another compound identified in our study KEM is a flavonoid found in different fruits and vegetables. KEM has been reported as a neuroprotector in AD by ameliorating oxidative stress and regulating the cholinergic system. KEM has been identified as a suppressor of inflammatory pathways in PD by inhibiting cytokine and chemokine production [447]. This compound has antioxidant properties and is thus known to increase dopamine levels and the endogenous levels of the com monly found free radical scavenging enzymes [448].

In conclusion, the natural compounds demonstrated potent neuroprotective activities by binding to CDK5 and GSK3B, the two important targets for AD and PD. Based on docking studies, API, SAL and SLY presented the best affinities for CDK5, while API, KEM, and SAL presented good binding results for GSK3B. Further, molecular dynamics simulation studies confirmed the CDK5 inhibitory potential of SAL and GSK3B inhibitory potential of KEM. However, experimental studies are required to validate the neuroprotective functions of the proposed natural compounds.

6.5 KEY HIGHLIGHTS OF THE STUDY

- ✓ 78 natural compounds were identified from the literature with anticancer properties
- ✓ 27 natural compounds were BBB permeable
- ✓ Salvianolic acid was founded a potent CDK5 inhibitor compound
- ✓ Kaempferol was found as a potent GSK3B inhibitor compound
- ✓ Salvianolic acid and kaempferol can be used for AD and PD treatment

CHAPTER VII

DISCUSSION, LIMITATIONS OF THE STUDY AND FUTURE PERSPECTIVES

CHAPTER VII: DISCUSSION, LIMITATIONS OF THE STUDY AND FUTURE PERSPECTIVES

7.1 DISCUSSION

Neurodegeneration and cancer share an exclusive association of genes and proteins involved in different signaling pathways. The shared mechanisms of various signaling pathways support the intriguing link between cancer, AD, PD, HD, ALS, and MS. Drug repositioning presents an electrifying opportunity for new drug development for NDDs. Currently, anticancer drugs are attaining more attraction for drug repurposing for NDDs. Based on the available literature, we found that anticancer drugs offer neuroprotective functions in different aspects as clearing toxic protein aggregation, resisting neuroinflammation, and immunomodulation. The major drug classes exhibiting promising repurposing results are- kinase inhibitors, antimetabolites, alkylating agents, and antibodies where kinase inhibitors are gaining most of the interest to date. Protein kinases have been identified to play a central role in several pathologies related to NDDs. The cellular and animal model studies have demonstrated the success of these small molecule drugs for NDDs and have encouraged their repurposing potential. However, the exact mechanistic role of these drugs in CNS diseases is still unknown and demands further investigation.

Drug repurposing is a productive approach to identifying novel therapeutic uses of available drugs. The common biological pathways of different diseases and the advancements in system biology tools open up new horizons to analyze the off-target effects of approved drugs for various indications. Over the last decade, several studies have been published, emphasizing the

shared molecular mechanism of AD, PD and cancer. Indeed, drug repurposing of anticancer drugs as neuroprotective agents has been applied to overcome AD and PD-related clinical consequences. However, the complexity of different neuropathological states and limited understanding of different cellular signaling mechanisms in AD and PD posed a big challenge to develop repurpose therapeutics.

The main goal of the current study was to investigate the repurposing potential of different approved anticancer drugs for AD and PD. The initial part of the study has identified the common mechanisms that exist between AD, PD and cancer by utilizing multi-omics approach. The second part of the study interrogated the relationship of PD and breast cancer and aimed to identify potential repurposed drugs. The last part of the study examined different anticancer drugs and natural compounds against different targets associated with AD and PD pathogenesis.

In the preliminary step, we leveraged publically available genomics, transcriptomics, and proteomics data to establish a relationship of AD and PD genes with cancer genes. From PPI, network-based approach and pathway analysis, we identified the connection of EGFR with AD-related targets such as APP, SNCA, LRP1, and NRG1 and PD-related targets such as LRRK2, MAPT, SH3GL2 and UCHL1. We developed a computational pipeline to identify the repurposing functions of various EGFR inhibitors in AD and PD. From CoDReS analysis, structural similarity, BBB permeability and literature-based analysis, erlotinib, gefitinib, and vandetanib were identified as repurposed EGFR inhibitors. The study has also identified miRNA200a as neuroprotective miRNAs for AD targeting EGFR and miRNA-409 and miRNA-7-3 as neuroprotective miRNAs for PD. We proposed that tau phosphorylation, autophagy, and neuroinflammation and Ca^{2+} signaling were the significant AD-related pathways targeted by the proposed drugs. Likewise, for PD, the repurposed drugs are proposed

to target α-syn aggregation, microgliosis, dopaminergic neurodegeneration, and mitochondrial dysfunction.

The second important finding of this study has been the identification of BRCA as the most closely related cancer with AD and PD in terms of shared genes and shared variants. Recently, a study has identified the relevance of different AD susceptibility genes in BRCA and APOE4 was co-occurrent with BRCA markers [449]. Similarly, a recently published study revealed that estrogen modulating therapies used in BRCA may reduce the risk of AD in female BRCA patients [450]. However, the link between PD and BRCA is not established yet and controversial studies are present. As far as the relation between PD and BRCA is not clear, we aimed to identify the relation between PD and BRCA. This study is the first to successfully apply the computational approach to manifest a relationship between PD and BRCA and to identify BRCA drugs for PD treatment based on multi-omics analysis. In this study, we tried to understand the disease-disease relationship by comparing genomics, transcriptomics and proteomics data and then extended this relationship to drug repurposing. We identified the common genes, regulatory molecules such as TFs and miRNAs and associated pathways. We utilized the application of Cmap database to identify the connection of available BRCA drugs with PD drugs and PD-related gene signatures. From CoDReS analysis, we identified raloxifene and tamoxifen as repurposed drugs for PD. Further, we proposed that these SERMs may provide neuroprotection by targeting neuroinflammation, dopaminergic neurodegeneration, mitochondrial dysfunction and protein aggregation in PD.

Another important observation of this study was that different anticancer drugs and natural compounds might target different enzymes regulating crucial processes related to AD and PD. We opted for a target-based drug repurposing approach based on virtual screening, molecular

docking and molecular dynamics simulations to screen anticancer drugs against MAOB enzyme. A number of bibliographic mentions have established the significance of MAOB inhibitors in PD and possibly AD treatment. Out of the 172 approved anticancer drugs, 40 drugs were found to interact with MAOB active site where three drugs- flutamide, imiquimod and thalidomide were showing best binding. Further, the molecular dynamics simulation study has confirmed the binding of these three drugs with imiquimod was showing the best results. This was the first study to confirm the potential of anticancer drug imiquimod as MAOB inhibitor.

To extend our drug repurposing analysis, we identified 78 natural compounds from the literature with reported anticancer activities. These natural compounds were screened against two different targets-CDK5 and GSK3B, which are commonly associated with the pathogenesis of both AD and PD. We reported 20 natural compounds showing good bindings with CDK5 active site and 13 compounds were interacting with GSK3B active site. Later, molecular dynamics simulations confirmed the biding potential of salvianolic acid with CDK5 and kaempferol with GDK3B. This suggests that natural products salvianolic acid and kaempferol may be used for AD and PD treatment.

To summarize, several significant outcomes have been achieved from this work. The most consequential finding was that the therapeutic targets known for cancer may also serve as potential targets for AD and PD. We identified the putative functions of EGFR, ER, CDK5 and GSK3B in neuroprotection and the anticancer drugs targeting these genes may regulate different signaling mechanisms associated with AD and PD **(Figure 7.1).** However, a thorough evaluation and experimental validation is a prerequisite to understanding the functions of these proposed repurposed drugs.

7.2 LIMITATIONS OF THE STUDY

The present study has several limitations. The study is based on a computational workflow based on different tools and filters used for result interpretation. However, the results may vary based on the type of tools used and the filters applied at different stages of the screening of drugs. The most important concern is the experimental validation of the proposed drugs. The results from the computational framework need validation under *in vitro* and/or *in vivo* conditions to confirm different parameters such as BBB permeability, enzymatic inhibition and therapeutic efficacy.

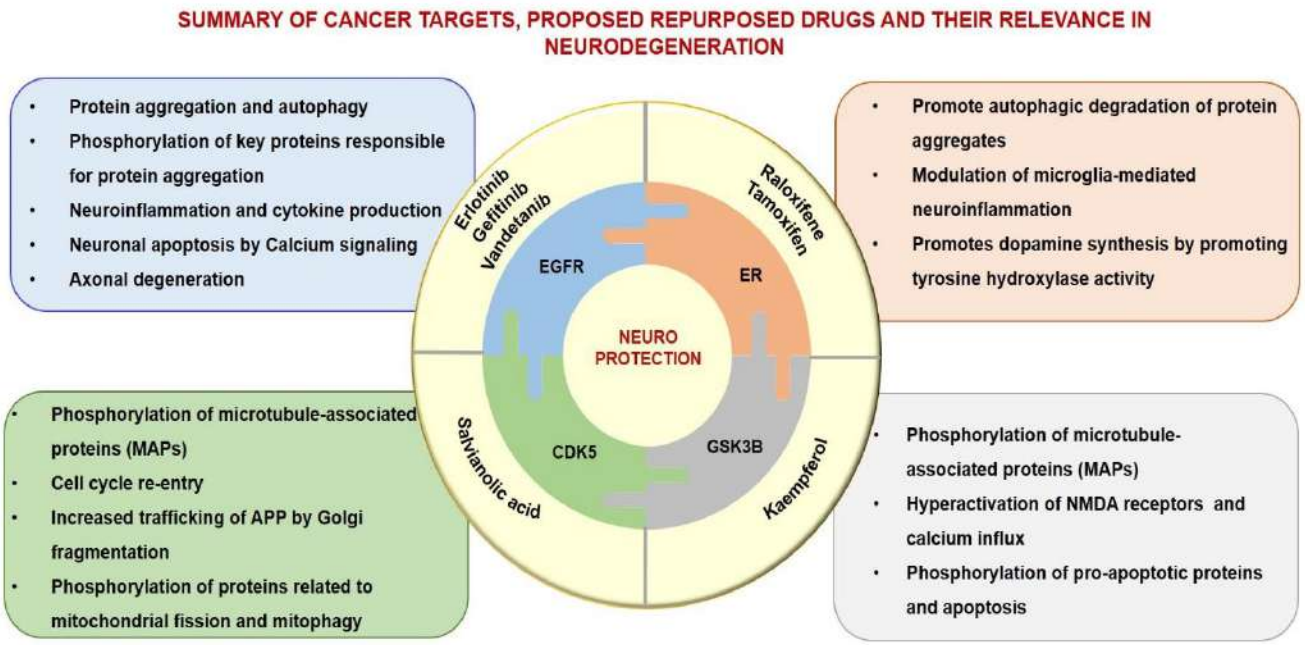


Figure 7.1: The neuropathological functions of cancer–related genes-EGFR, ER, CDK5, and GSK3B in AD and PD, along with the proposed repurposed drugs identified in the study

7.3 FUTURE PERSPECTIVES

- An integrated analysis of multi-omics data for AD, PD and cancer not only facilitates drug development process but also helps to comprehend better the intriguing, rather complex relationship of neurodegeneration and cancer.
- The findings of this thesis can further be extended to identify the disease-disease relationship among different indications and the identified common mechanisms can be targeted from the perspective of drug repurposing.
- The study opens up new avenues for novel biomarker identification for AD and PD. These biomarkers can be exploited to develop novel therapeutic regimens.
- The pipeline presented in the study would be extremely useful for identifying the repurposing potential of drugs other than anticancer drugs that are approved for various indications for the treatment of AD and PD.
- The ultimate aim of this study is to explore the repurposing potential of anticancer drugs by using computational methods. We hope that the proposed drugs might present opportunistic results under experimental conditions. For this, cell-based and animal-based studies would be of great benefit in investigating the biological relevance of the identified repurposed drugs in the new indication. To sum up, we believe that the experimental validation of our initial studies would help to complete our ongoing quest to uncover novel therapies for AD and PD treatment.

ANNEXURES

Annexure 1: List of AD and PD-associated genes identified after functional enrichment analysis

AD-associated genes	PD-associated genes
ACE	APOE
ACHE	ATP13A2
ALOX5	BDNF
APOC1	BST1
APOE	CCDC62
APP	CP
BCHE	CSMD1
BIN1	DGKQ
CDK5	FBXO7
CH25H	FGF20
CHAT	FUS
CLU	FYN
COMT	GAK
CP	GBA
CR1	GCH1
CYP2D6	GIGYF2
CYP46A1	GRN
DAPK1	GSTO2
DRD1	HIP1R
DRD3	HTRA2
DRD4	ITGA8
EXOC3L2	KANSL1
FYN	LINGO1
GAD2	LRRK2
GRIN2B	MAPT
GSK3B	MCCC1
GST1	MMRN1
GST2	MT-ND1
HSPG2	MT-ND3
HTR2AQ	NDUFS4
HTR2C	NDUFV2
IDE	NUCKS1
LRP1	PACRG
MME	PARK7
NECTIN2	PINK1
NEDD9	PITX3
NRG1	PLA2G6
PCDH11X	POLG
PCK1	PRKN
PLCALM	RAB29
PLD3	RIT2

PSEN1	SH3GL2
SIGMAR1	SIAH1
SNAP25	SLC41A1
SNCA	SNCA
TF	SNCAIP
TOMM40	SNCB
TPH1	STBD1
VSNL1	SYT11
	TFB2M
	TH
	TMEM175
	UCHL1
	VPS41

Annexure 2: List of FDA approved anticancer drugs used in the study (172 drugs)

S. No.	Drug name	S.No.	Drug name
1	Abemaciclib	87	Lanreotide Acetate
2	Abiraterone Acetate	88	Lapatinib Ditosylate
3	Acalabrutinib	89	Larotrectinib Sulfate
4	Afatinib Dimaleate	90	Lenalidomide
5	Alectinib	91	Lenvatinib Mesylate
6	Alpelisib	92	Letrozole
7	Anastrozole	93	Leucovorin Calcium
8	Apalutamide	94	Leuprolide Acetate
9	Arsenic Trioxide	95	Lomustine
10	Avapritinib	96	Lorlatinib
11	Axitinib	97	Lurbinectedin
12	Azacitidine	98	Mechlorethamine Hydrochloride
13	Belinostat	99	Megestrol Acetate
14	Bendamustine Hydrochloride	100	Melphalan
15	Bexarotene	101	Mercaptopurine
16	Bicalutamide	102	Methotrexate Sodium
17	Binimetinib	103	Midostaurin
18	Bleomycin Sulfate	104	Mitomycin
19	Bortezomib	105	Mitoxantrone Hydrochloride
20	Bosutinib	106	Nelarabine
21	Brigatinib	107	Neratinib Maleate
22	Busulfan	108	Nilotinib
23	Cabazitaxel	109	Nilutamide
24	Cabozantinib-S-Malate	110	Niraparib Tosylate Monohydrate
25	Capecitabine	111	Olaparib
26	Capmatinib Hydrochloride	112	Omacetaxine Mepesuccinate
27	Carboplatin	113	Ondansetron Hydrochloride
28	Carfilzomib	114	Osimertinib Mesylate

29	Carmustine	115	Oxaliplatin
30	Ceritinib	116	Paclitaxel
31	Chlorambucil	117	Palbociclib
32	Cisplatin	118	Panobinostat Lactate
33	Cladribine	119	Pazopanib Hydrochloride
34	Clofarabine	120	Pemetrexed Disodium
35	Cobimetinib Fumarate	121	Pemigatinib
36	Copanlisib Hydrochloride	122	Pexidartinib Hydrochloride
37	Crizotinib	123	Plerixafor
38	Cyclophosphamide	124	Pomalidomide
39	Cytarabine	125	Ponatinib Hydrochloride
40	Dabrafenib Mesylate	126	Pralatrexate
41	Dacarbazine	127	Pralsetinib
42	Dacomitinib	128	Prednisone
43	Dactinomycin	129	Procarbazine Hydrochloride
44	Darolutamide	130	Raloxifene Hydrochloride
45	Dasatinib	131	Regorafenib
46	Daunorubicin Hydrochloride	132	Relugolix
47	Decitabine	133	Ribociclib
48	Degarelix	134	Ripretinib
49	Dexamethasone	135	Romidepsin
50	Dexrazoxane Hydrochloride	136	Rucaparib Camsylate
51	Docetaxel	137	Ruxolitinib Phosphate
52	Doxorubicin Hydrochloride	138	Selinexor
53	Duvelisib	139	Selpercatinib
54	Enasidenib Mesylate	140	Selumetinib Sulfate
55	Encorafenib	141	Sonidegib
56	Entrectinib	142	Sorafenib Tosylate
57	Enzalutamide	143	Sunitinib Malate
58	Epirubicin Hydrochloride	144	Talazoparib Tosylate
59	Erdafitinib	145	Tamoxifen Citrate
60	Eribulin Mesylate	146	Tazemetostat Hydrobromide
61	Erlotinib Hydrochloride	147	Tepadina (Thiotepa)
62	Etoposide	148	Tepotinib Hydrochloride
63	Everolimus	149	Thalidomide
64	Exemestane	150	Thioguanine
65	Fedratinib Hydrochloride	151	Tivozanib Hydrochloride
66	Fludarabine Phosphate	152	Topotecan Hydrochloride
67	Fluorouracil	153	Toremifene
68	Flutamide	154	Torisel (Temsirolimus)
69	Fostamatinib Disodium	155	Trabectedin
70	Fulvestrant	156	Trametinib Dimethyl Sulfoxide
71	Gefitinib	157	Trifluridine

72	Gemcitabine Hydrochloride	158	Tipiracil
73	Gilteritinib Fumarate	159	Tucatinib
74	Glasdegib Maleate	160	Umbralisib Tosylate
75	Goserelin Acetate	161	Uridine Triacetate
76	Hydroxyurea	162	Valrubicin
77	Ibrutinib	163	Vandetanib
78	Idarubicin Hydrochloride	164	Vemurafenib
79	Idelalisib	165	Venetoclax
80	Ifosfamide	166	Vinblastine Sulfate
81	Imatinib Mesylate	167	Vincristine Sulfate
82	Imiquimod	168	Vinorelbine Tartrate
83	Irinotecan Hydrochloride	169	Vismodegib
84	Ivosidenib	170	Vorinostat
85	Ixabepilone	171	Zanubrutinib
86	Ixazomib Citrate	172	Zoledronic Acid

Annexure 3: List of Alzheimer's and Parkinson's drugs used in the study

S.No.	Alzheimer's Drugs	Parkinson's Drugs
1	Donepezil	Apomorphine
2	Galantamine	Amantadine
3	Memantine	Benztropine
4	Rivastigamine	Carbidopa
5		Entacapone
6		Istradefylline
7		Levadopa
8		Opicapone
9		Pramipexole
10		Rasagiline
11		Ropinirole
12		Rotigotine
13		Safinamide
14		Selegiline
15		Tolcapone
16		Trihexyphenidyl

Annexure 4: Physiochemical properties of potential repurposing drugs

Drug name	MW	RB	HBA	HBD	TPSA	M log P	BBB
Afatinib	485.94	9	7	2	88.61	2.43	No
Erlotinib	393.44	10	6	1	74.73	1.89	Yes
Gefitinib	446.9	8	7	1	68.74	2.82	Yes
Imatinib	439.6	8	6	2	86.28	2.15	No
Sunitinib	398.47	8	4	3	77.23	2.06	Yes
Vandetanib	475.35	6	6	1	59.51	3.45	Yes

Abbreviations: MW: Molecular weight; RB: Rotatable bonds; HBA: Hydrogen bond acceptor; HBD: Hydrogen bond donor; TPSA: Total polar surface area;
*Highlighted drugs have good drug-likeness and BBB permeation

Annexure 5: List of common genes between Parkinson's disease and breast cancer identified from three different omics layers

GENOMICS	TRANSCRIPTOMICS	PROTEOMICS	COMMON GENES
PTPRD	SNORA72	EIF4G1	AREG
WNT3	TIFAB	ATP6	ATP6
ZNF165	HEATR9	ND5	ATP8
FBRSL1	CD177	ND4L	BIN3
SV2C	HSPA1B	ND3	BMP7
NSF	SAA2	**BMP7**	C7orf61
TRPS1	LINC01068	ND4	CAV1
UBTF	FCRL1	COX2	CCL3L1
ZSCAN12P1	MMP8	ND6	CCL4L2
SLC25A44	TAS2R50	COX3	CD177
DLG2	WDR64	RNF11	COL5A2
SEMA5A	LOC101928978	SQSTM1	COX1
WWOX	FAM41C	PODXL	COX2
BIN3	EDRF1-AS1	NOS2	COX3
TRIM46	DDX11L16	REST	CXCL8
TOX3	LOC105378044	ND2	CYP24A1
KIAA1967	C7orf61	CYTB	CYTB
DPM3	SH2D1B	ND1	DDX11L16
KRTCAP2	OTOR	ATP8	DLG2
MRPS30	LOC100505664	COX1	DPM3
COL5A2	FOSB	CAV1	DUSP2
TBX2	EGR2	FOXRED1	EDRF1-AS1
PLEKHH1	CYP24A1	KLK6	EFNA1

EFNA1	NEUROD2	MFN1	EGR2
SLC50A1	DUSP2	NDUFA1	EIF4G1
RAI1	PSMA8	NDUFA2	FAM41C
SREBF1	IBSP	NDUFAF4	FBRSL1
BMP7	LOC153910	NEK2	FCRL1
	IL6	HOOK1	FOSB
	CXCL8		FOXRED1
	LILRB2		HEATR9
	MDC1		HLA-C
	CCL3L1		HOOK1
	AREG		HSPA1B
	LINC01164		IBSP
	RNF39		IL1B
	SNORD116-5		IL6
	IL1B		KIAA1967
	HLA-C		KLK6
	CCL4L2		KRTCAP2
			LILRB2
			LINC01068
			LINC01164
			LOC100505664
			LOC101928978
			LOC105378044
			LOC153910
			MDC1
			MFN1
			MMP8
			MRPS30
			ND1
			ND2
			ND3
			ND4
			ND4L
			ND5
			ND6
			NDUFA1
			NDUFA2
			NDUFAF4
			NEK2
			NEUROD2
			NOS2
			NSF
			OTOR
			PLEKHH1

			PODXL PSMA8 PTPRD RAI1 REST RNF11 RNF39 SAA2 SEMA5A SH2D1B SLC25A44 SLC50A1 SNORA72 SNORD116-5 SQSTM1 SREBF1 SV2C TAS2R50 TBX2 TIFAB TOX3 TRIM46 TRPS1 UBTF WDR64 WNT3 WWOX ZNF165 ZSCAN12P1

***Genes in bold are common in more than one approach.**

Annexure 6: Relation of breast cancer drugs with PD gene signatures identified from Cmap.

Final PD genes	**ALP**	**ANA**	**CYC**	**DOXO**	**EVE**	**FU**	**LAP**	**MXR**	**NER**	**OLA**	**PAB**	**RA**	**TX**	**TH**	**TOR**
APOE	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ATP13A2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
BDNF	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
BST1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CCDC62	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CCK	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CP	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CSMD1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CYP17A1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

DGKQ	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FBXO7	N/A	0	43.94	29.57	0	N/A	-39.95	N/A	76.2	23.05	20.79	-49.22	36.64	29.1	0
FDFT1	N/A	0	67.46	52.69	62.25	N/A	0	71.67	42.11	-18.84	0	64.09	43.51	-58.98	52.94
FGF20	N/A	N/A	N/A	N/A	N/A	N/A	N/A	20	N/A	N/A	0	N/A	N/A	N/A	N/A
FYN	N/A	66.1	20.79	22.6	22.61	N/A	89.45	0	0	0	N/A	0	N/A	24.58	0
GAK	N/A	N/A	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
GBA	N/A	98.52	0	-49.95	0	N/A	97.27	-51.39	0	85.38	38.48	0	0	89.26	0
GCH1	N/A	N/A	N/A	N/A	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
GIGYF2	N/A	N/A	N/A	N/A	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
GRN	N/A	0	76.58	89.95	42.12	N/A	81.53	83.49	89.17	48.89	67.94	72.16	N/A	60.03	64.3
GSTO2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HIP1R	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HTRA2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
IL1RN	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ITGA8	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
KANSL1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LINGO1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LRRK2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
MAPT	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
MCCC1	N/A	52.42	48.52	26.16	-80.13	N/A	0	0	0	0	0	0	-96.27	0	-60.97
MMRN1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
NDUFS4	N/A	29.04	0	64.31	0	N/A	59.81	29.64	87.8	48.99	26.06	0	0	57.23	48.43
NDUFV2	N/A	0	-56.44	0	N/A	N/A	0	-60.46	0	82.03	-45.1	-37.82	35.15	92.8	49.86
NOD2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
NUCKS1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PACRG	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PARK2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PARK7	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PINK1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PITX3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PLA2G6	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
POLG	N/A	33.61	54.82	0	67.4	N/A	26.46	0	90.98	60.83	49.93	N/A	24.79	24.92	0
PRSS53	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
RAB25	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
RAB29	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
RIT2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SCN2A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SH3GL2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SIAH1	N/A	33.61	87	89.21	0	N/A	56.34	94.95	98.19	-22.69	-45.82	40.36	23.26	-24.39	54.83
SLC2A13	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SLC41A1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SLC45A3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SNCA	N/A	0	-44.54	0	0	N/A	79.03	-32.04	0	45	63.72	51.3	0	43.52	0

SNCAIP	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SNCB	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
STAP1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
STBD1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
STK39	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SYT11	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TFB2M	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TMEM108	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TMEM163	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TMEM175	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
UCHL1	N/A	42.21	0	-67	0	N/A	67.02	-86.4	0	72.32	-26.21	0	0	86.31	-40.22
UNC13B	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
VPS41	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ZNF646	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: ALP: Alpelisib; ANA: Anastrazole; CYC: Cyclophosphamide; DOXO: Doxorubicin; EVE: Everolimus; FU: Fluorouracil; LAP: Lapatinib; MXR: Mitoxantrone; NER: Neratinib; OLA: Olaparib; PAB: Palbociclib; RA: Raloxifene; TX: Tamoxifen; TH: Thiotepa; TOR: Toremifene

The negative values are highlighted in red, while the positive values are highlighted in yellow

Annexure 7: List of Parkinson's disease and breast cancer drugs used in the study

S.No.	Breast cancer drugs	S.No.	Breast cancer drugs
1	Abemaciclib	20	Lapatinib Ditosylate
2	Alpelisib	21	Letrozole
3	Anastrozole	22	Megestrol Acetate
4	Buserlin	23	Methotrexate Sodium
5	Capecitabine	24	Mitoxantrone
6	Carboplatin	25	Neratinib Maleate
7	Cisplatin	26	Olaparib
8	Cyclophosphamide	27	Paclitaxel
9	Docetaxel	28	Palbociclib
10	Doxorubicin Hydrochloride	29	Pamidronate
11	Epirubicin Hydrochloride	30	Raloxifene Hydrochloride
12	Eribulin Mesylate	31	Ribociclib
13	Everolimus	32	Talazoparib Tosylate
14	Exemestane	33	Tamoxifen Citrate
15	Fluorouracil	34	Thiotepa
16	Fulvestrant	35	Toremifene
17	Gemcitabine Hydrochloride	36	Tucatinib
18	Goserelin Acetate	37	Vinblastine Sulfate
19	Ixabepilone	38	Vinorelbine

Annexure 8: Docking scores of the anticancer drugs with MAOB enzyme

S.No.	Anticancer drug	Docking scores
1	Imiquimod	-8.5
2	Thalidomide	-8.1
3	Flutamide	-8
4	Vorinostat	-7.3
5	Clofarabine	-6.9
6	Thiotepa	-6.3
7	Thioguanine	-6.3
8	Carmustine	-5.9
9	Cyclophosphamide	-5.9
10	Busulfan	-5.7
11	Ifosfamide	-5.5
12	Lenalidomide	-5.1
13	Anastrozole	-2.7
14	Exemestane	2.1
15	Letrozole	2.2
16	Selinexor	13.5
17	Prednisone	18.4
18	Dexamethasone	22.3
19	Axitinib	29.9
20	Vandetanib	48.7
21	Erdafitinib	51.9

Annexure 9 : List of natural compounds used for this study

Compound name	PubChem ID	Compound class
Allicin	65036	Sulfoxide
Alpinumisoflavone	5490139	Flavonoid
Andrographolide	5318517	Lipid
Apigenin	5280443	Flavonoid
Artemisinin	68827	Lactone
Artesunate	6917864	Lactone
Astaxanthin	5281224	Lipid
Baicalin	64982	Flavonoid
Berberine	2353	Alkaloid
Beta-elemene	6918391	Terpene
Betulinic acid	64971	Terpene
Bilobetin	5315459	Flavonoid
Borbonol	10448019	Nitro compound

Capsaicin	1548943	Phenol
Cepharanthine	10206	Isoquinoline
Chamomillol	91747197	Terpene
Colchicine	6167	Alkaloid
Combrestastatin	5467057	Phenol
Crocetin	5281232	Terpene
Crocin	5281233	Terpene
Cryptotanshinone	160254	Terpene
Cucurbitacin	5281316	Steroid
Curcumin	969516	Phenol
Decursinol	442127	Organic heterocyclic
Dicoumarol	54676038	Coumarin
EGCG	65064	Phenol
Emodin	3220	Anthrone
Epicatechin	72276	Phenol
Gambogic acid	9852185	Aromatic
Genipin	442424	Beta-hydroxy ketone
Geniposide	107848	Terpene
Genistein	5280961	Flavonoid
Gingerol	442793	Phenol
Ginkgetin	5271805	Flavonoid
Ginseng	10253669	Terpene
Glycyrrhizin	14982	Terpene
Grisemycin	132919089	Organic compound
Hispidulin	5281628	Flavonoid
Icarin	5471129	Flavonoid
Ingenol	442042	Terpene
Isoginkgetin	5318569	Flavonoid
Kaempferol	5280863	Flavonoid
Licoagrochalcone	5318989	Chalcone
Licochalcone	9840805	Chalcone
Luteolin	5280445	Flavonoid
Lycopene	446925	Carotenoid
Melatonin	896	Indole
Metformin	4091	Organic compound
Moromycin B	25112054	Organic compound
Nimbolide	12313376	Terpene
Nosacapine	275196	Alkaloid
Oridonin	5321010	Terpene
Panaxadiol	73498	Phenol
Paradol	94378	Phenol
Physapubescin B	72199040	Steroid
Pterostilbene	5281727	Phenol

Quercetin	5280343	Flavonoid
Resveratrol	445154	Phenol
Rutin	5280805	Flavonoid
Safranal	61041	Phenol
Salvianolic acid	5281793	Coumaric acid
Salvicin	6439003	Beta-glucoside
Saquayamycin	127271	Organic compound
Shikonin	479503	Quinone
Shogaol	5281794	Phenol
Silibinin	31553	Flavonolignan
Silymarin	5213	Flavonoid
Sulphoraphane	5350	Isothiocynate
Tannic acid	16129778	Tannin
Tanshinone	114917	Terpene
Thymol	6989	Phenol
Thymoquinone	10281	Quinone
Triptolide	107985	Terpene
Ursolic acid	64945	Terpene
Violaceomide	156581760	Organic compound
Withaferin	265237	Alcohol
Wogonin	5281703	Flavonoid

Annexure 10: Toxicity analysis of the natural compounds

Natural product	Hepato-toxicity	Muta-genicity	Carcino-genicity	Immuno-Toxicity	Cyto-toxicity	Toxicity class	LD50 (mg/kg)
Apigenin	No	No	No	No	No	Non-toxic	2500
Allicin	No	No	No	No	No	Moderate	874
Borbonol	No	No	No	Yes	No	Non-toxic	1000000
Beta-elemene	No	No	No	No	No	Non-toxic	5000
Chamomillol	No	No	No	Yes	No	Moderate	890
Cryptotanshinone	No	No	yes	Yes	No	Non-toxic	4000
Cepharanthine	No	Yes	Yes	Yes	Yes	Moderate	1900
Capsaicin	No	Yes	Yes	Yes	No	Toxic	47
Gingerol	No	No	No	Yes	No	Moderate	250
Genipin	No	No	No	No	No	Moderate	237
Kaempferol	No	No	No	No	No	Non-toxic	3919
Melatonin	No	No	No	No	No	Moderate	963
Noscapine	No	No	Yes	Yes	Yes	Moderate	840
Paradol	No	Yes	No	Yes	No	Non-toxic	2580
Pterostilbene	No	No	No	Yes	No	Moderate	1560
Resveratrol	No	No	No	No	No	Moderate	1560

Sulforaphane	No	No	No	No	No	Moderate	1000
Safranal	Yes	No	No	Yes	No	Moderate	1190
Salvianolic acid	No	No	No	Yes	No	Non-toxic	5000
Silymarin	No	No	No	yes	No	Moderate	2000
Shogaol	No	Yes	No	Yes	No	Moderate	687
Salvicin	No	No	No	yes	No	Non-toxic	9000
Thymol	No	No	No	No	No	Moderate	640
Thymoquinone	No	No	No	No	No	Non-toxic	2400
Triptolide	No	Yes	No	Yes	No	Toxic	4
Tanshinone	No	No	No	No	No	Moderate	1655
Ursolic acid	Yes	No	Yes	Yes	No	Moderate	2000

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LIST OF PUBLICATIONS

Cumulative impact factor of all publications	=**34.58**
h-index and i-10 index	=**4 and 1**
Cumulative citation index	=**45**

PUBLICATIONS FROM THESIS

1. **Dia Advani** and Pravir Kumar. "Deciphering the molecular mechanism and crosstalk between Parkinson's disease and breast cancer through multi-omics and drug repurposing approach." *Neuropeptides*, vol. 96 102283. 17 Aug. 2022, doi:10.1016/j.npep.2022.102283. IF: 3.286 (Elsevier)

2. **Dia Advani** and Pravir Kumar. "Therapeutic Targeting of Repurposed Anticancer Drugs in Alzheimer's Disease: Using the Multiomics Approach." *ACS omega* vol. 6,21 13870-13887. 19 May. 2021, doi:10.1021/acsomega.1c01526. IF: 4.13 (ACS)

3. **Dia Advani**, Rohan Gupta, Rahul Tripathi, Sudhanshu Sharma, Rashmi K Ambasta, and Pravir Kumar. "Protective role of anticancer drugs in neurodegenerative disorders: A drug repurposing approach." *Neurochemistry international* vol. 140 (2020): 104841. doi:10.1016/j.neuint.2020.104841IF: 4.29 (Elsevier)

OTHER PUBLICATIONS

1. **Dia Advani**, Sudhanshu Sharma, Smita Kumari, Rashmi K Ambasta, and Pravir Kumar "Precision Oncology, Signaling, and Anticancer Agents in Cancer Therapeutics." *Anti-cancer agents in medicinal chemistry* vol. 22,3 (2022): 433-468.

doi:10.2174/1871520621666210308101029IF: 2.527 (Bentham)

2. Smita Kumari, **Dia Advani**, Sudhanshu Sharma, Rashmi K Ambasta, and Pravir Kumar "Combinatorial therapy in tumor microenvironment: Where do we stand?." *Biochimica et biophysica acta. Reviews on cancer* vol. 1876,2 (2021): 188585. doi:10.1016/j.bbcan.2021.188585. Combinatorial therapy in tumor microenvironment: where do we stand? Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2021 Dec 1;1876(2):188585. DOI: 10.1016/j.bbcan.2021.188585. IF: 11.41 (Elsevier)

3. Smita Kamari, Sudhanshu Sharma, **Dia Advani**, Aakansha Khosla, Pravir Kumar, and Rashmi K Ambasta."Unboxing the molecular modalities of mutagens in cancer." *Environmental science and pollution research international* vol. 29,41 (2022): 62111-62159. doi:10.1007/s11356-021-16726-wIF: 5.19 (Springer)

4. Sudhanshu Sharma, **Dia Advani**, Ankita Das, Nishtha Malhotra, Aakansha Khosla, Vanshika Arora, Ankita Jha, Megha Yadav, Rashmi K Ambasta, and Pravir Kumar. "Pharmacological intervention in oxidative stress as a therapeutic target in neurological disorders." *The Journal of pharmacy and pharmacology* vol. 74,4 (2022): 461-484. doi:10.1093/jpp/rgab064. . IF: 3.765 (Wiley)

BOOK CHAPTERS

1. **Dia Advani**, Sudhanshu Sharma, Rahul Tripathi, Rohan Gupta, Asmita Jaiswal, Rashmi K Ambasta, and Pravir Kumar, "Mitochondrial dysfunction in metabolic disorders", "Mitochondrial Dysfunction and Nanotherapeutics (Elsevier), Aging, Diseases, and Nanotechnology-Related Strategies in Mitochondrial Medicine"

CONFERENCE PROCEEDINGS

1. **Dia Advani** and Pravir Kumar (2019), Protective role of c-Abl inhibitors in neurological disorders: An *in silico* drug repurposing approach, SNCI October 2019, Jamia Hamdard, Delhi, India. [Poster presentation]

2. **Dia Advani** and Pravir Kumar (2022), Computational analysis of natural compounds as cyclin-dependent kinase-5 inhibitors for Alzheimer's and Parkinson's Disease, SNCI 2022, GUCON 2022 — IEEE 5th International Conference on Computing, Power and Communication Technologies, New Delhi, India. [Oral Presentation]

WORKSHOPS ATTENDED

1. One week DST STUTI Hands-On training program on Biological Electron Microscopy at AlIMS, New Delhi, from 29th August to 4th September 2022
2. One-month online workshop on Drug Discovery And Development organized by Decode LifeSciences, 21st May to 15th June, 2022
3. Post-conference workshop on "Neurological Disorders: Advances in Research Techniques and Translational Applications", 13th to 19th October 2019, SNCI, Jamia Hamdard, Delhi, India.

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EDUCATIONAL BACKGROUND

INSTITUTION	POSITION	YEAR	FIELD OF STUDY
Delhi Technological University (Formerly DCE), Delhi	Ph.D. (Senior Research Fellow)	2018-present	Neuroscience (Biotechnology)
Jai Narain Vyas University, Jodhpur	M.Sc. Biotechnology	2012-2014	Biotechnology
Jai Narain Vyas University, Jodhpur	B.Sc. Biotechnology	2009-2012	Biotechnology

PERSONAL STATEMENT

My interest in science dates back to my undergraduate and postgraduate studies, where I began my career in the field of biotechnology. In my Ph.D., I have started my scientific endeavors with a special focus in the field of neuroscience. During this tenure, I gained experience in multiple disciplines such as neurobiology, computational biology, molecular biology, integrated omics, and drug discovery and development. I have developed a special interest in drug development and focused my doctoral thesis on repurposing anticancer drugs in neurodegenerative disorders. As a doctoral student, I have followed the research being conducted by Prof. Pravir Kumar and aimed to contribute to the research world under his supervision. My doctoral research was specifically focused on understanding the complex overlapping mechanisms of cancer and neurodegeneration and to elaborate this knowledge to identify potent neuroprotective anticancer drugs for various neurodegenerative disorders. During this period, I have published different papers in reputed scientific journals including Neurochemistry International, ACS OMEGA, and Neuropeptides. I have attended different conferences and workshops to strengthen my research background to get exposure to the scientific world. Following completion of my Ph.D., I aim to move directly to

postdoctoral studies to leverage my skills and research experience in the field of neuroscience. I strongly believe that by utilizing my theoretical and practical experience, I can make the most significant contribution in the field of research and development.

AWARDS

- Senior research fellow (SRF), Department of Biotechnology, Govt. of India (2020-present)
- Junior research fellow (JRF), Department of Biotechnology, Govt. of India (2018)
- Council of Scientific and Industrial Research National Eligibility Test (NET) Junior Research Fellow award (2015)

PEER-REVIEWED PUBLICATIONS

Cumulative impact factor of all publications	=	**34.58**
h-index and i-10 index	=	**4 and 1**
Cumulative citation index	=	**45**

FIRST AUTHOR PUBLICATIONS

- **Dia Advani** and Pravir Kumar. "Deciphering the molecular mechanism and crosstalk between Parkinson's disease and breast cancer through multi-omics and drug repurposing approach." *Neuropeptides*, vol. 96 102283. 17 Aug. 2022, doi:10.1016/j.npep.2022.102283. IF: 3.286 (Elsevier)
- **Dia Advani** and Pravir Kumar. "Therapeutic Targeting of Repurposed Anticancer Drugs in Alzheimer's Disease: Using the Multiomics Approach." *ACS omega* vol. 6,21 13870-13887. 19 May. 2021, doi:10.1021/acsomega.1c01526. IF: 4.13 (ACS)
- **Dia Advani**, Rohan Gupta, Rahul Tripathi, Sudhanshu Sharma, Rashmi K Ambasta, and Pravir Kumar. "Protective role of anticancer drugs in neurodegenerative disorders: A drug repurposing approach." *Neurochemistry international* vol. 140 (2020): 104841. doi:10.1016/j.neuint.2020.104841IF: 4.29 (Elsevier)
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CO-AUTHOR PUBLICATIONS

- Smita Kumari, Dia Advani, Sudhanshu Sharma, Rashmi K Ambasta, and Pravir Kumar "Combinatorial therapy in tumor microenvironment: Where do we stand?." Biochimica et biophysica acta. Reviews on cancer vol. 1876,2 (2021): 188585.

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- Smita Kamari, Sudhanshu Sharma, **Dia Advani**, Aakansha Khosla, Pravir Kumar, and Rashmi K Ambasta."Unboxing the molecular modalities of mutagens in cancer." *Environmental science and pollution research international* vol. 29,41 (2022): 62111-62159. doi:10.1007/s11356-021-16726-wIF: 5.19 (Springer)

- Sudhanshu Sharma, **Dia Advani**, Ankita Das, Nishtha Malhotra, Aakansha Khosla, Vanshika Arora, Ankita Jha, Megha Yadav, Rashmi K Ambasta, and Pravir Kumar. "Pharmacological intervention in oxidative stress as a therapeutic target in neurological disorders." *The Journal of pharmacy and pharmacology* vol. 74,4 (2022): 461-484. doi:10.1093/jpp/rgab064. IF: 3.765 (Wiley)

BOOK CHAPTERS

- **Dia Advani**, Sudhanshu Sharma, Rahul Tripathi, Rohan Gupta, Asmita Jaiswal, Rashmi K Ambasta, and Pravir Kumar, "Mitochondrial dysfunction in metabolic disorders", "Mitochondrial Dysfunction and Nanotherapeutics (Elsevier), Aging, Diseases, and Nanotechnology-Related Strategies in Mitochondrial Medicine"

CONFERENCE PROCEEDINGS

- **Dia Advani** and Pravir Kumar (2019), Protective role of c-Abl inhibitors in neurological disorders: An in silico drug repurposing approach, SNCI October 2019, Jamia Hamdard, Delhi, India. [Poster presentation]

- **Dia Advani** and Pravir Kumar (2022), Computational analysis of natural compounds as cyclin-dependent kinase-5 inhibitors for Alzheimer's and Parkinson's Disease, SNCI 2022, GUCON 2022 — IEEE 5th International Conference on Computing, Power and Communication Technologies, New Delhi, India. [Oral Presentation]

WORKSHOPS ATTENDED

- One week DST STUTI Hands-On training program on Biological Electron Microscopy at AlIMS, New Delhi, from 29th August to 4th September 2022

- One-month online workshop on Drug Discovery And Development organized by Decode LifeSciences, 21st May to 15th June, 2022

- Post-conference workshop on "Neurological Disorders: Advances in Research Techniques and Translational Applications", 13th to 19th October 2019, SNCI, Jamia

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MEMBERSHIPS

Society of Neurochemistry India (SNCI), (India)-Life member

TECHNICAL EXPERIENCE

Bioinformatics – sequence searching and alignment (BLAST, CLUSTAL), multi-omics data analysis, auto dock, integrated database search

Experimental – DNA isolation, SDS page, qualitative and quantitative estimation of proteins and carbohydrates, sub culturing of cell, drug screening, cell viability assays (trypan blue exclusion test, MTT assay), microscopic work, SDS-page and western blotting

STRENGTHS

Confidence, teamwork spirit, dedication to work

PERSONAL DETAILS

Date of birth: 11th October 1992

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DECLARATION

I hereby declare that all the particulars above are accurate to my knowledge and understanding.

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Therapeutic Targeting of Repurposed Anticancer Drugs in Alzheimer's Disease: Using the Multiomics Approach

Dia Advani and Pravir Kumar*

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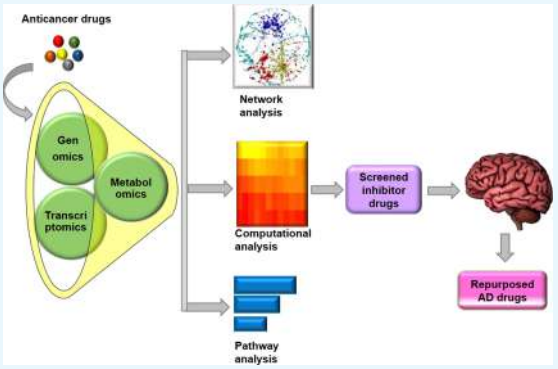
ABSTRACT: Aim/Hypothesis: The complexity and heterogeneity of multiple pathological features make Alzheimer's disease (AD) a major culprit to global health. Drug repurposing is an inexpensive and reliable approach to redirect the existing drugs for new indications. The current study aims to study the possibility of repurposing approved anticancer drugs for AD treatment. We proposed an *in silico* pipeline based on "omics" data mining that combines genomics, transcriptomics, and metabolomics studies. We aimed to validate the neuroprotective properties of repurposed drugs and to identify the possible mechanism of action of the proposed drugs in AD. Results: We generated a list of AD-related genes and then searched DrugBank database and Therapeutic Target Database to find anticancer drugs related to potential AD targets. Specifically, we researched the available approved anticancer drugs and excluded the information of investigational and experimental drugs. We developed a computational pipeline to prioritize the anticancer drugs having a close association with AD targets. From data mining, we generated a list of 2914 AD-related genes and obtained 49 potential druggable targets by functional enrichment analysis. The protein−protein interaction (PPI) studies for these genes revealed 641 interactions. We found that 15 AD risk/direct PPI genes were associated with 30 approved oncology drugs. The computational validation of candidate drug−target interactions, structural and functional analysis, investigation of related molecular mechanisms, and literature-based analysis resulted in four repurposing candidates, of which three drugs were epidermal growth factor receptor (EGFR) inhibitors. Conclusion: Our computational drug repurposing approach proposed EGFR inhibitors as potential repurposing drugs for AD. Consequently, our proposed framework could be used for drug repurposing for different indications in an economical and efficient way.



1. INTRODUCTION

The alarming progression rate, limited therapeutics, and the slow pace of new drug development for Alzheimer's disease (AD) draw the attention of research groups and pharmaceutical companies toward exploring new alternatives. Conventionally, AD is denoted as a central nervous system (CNS) disorder characterized by abnormal amyloid-β (Aβ) aggregation, tangle formation of hyperphosphorylated tau, oxidative stress, and hyperactivity glial and microglial cells.[1] The latest reports by the Alzheimer's association suggested that five FDA-approved drugs are currently marketed for AD.[2] The failure rate of AD therapeutics is more than 99%, and for the disease-modifying therapies, it is 100%. It has been a matter of more than 20 years; no new drug is licensed for AD. The research community is continuously involved in developing new drug discovery strategies; one of the examples is drug repurposing. To encourage the use of repurposed drugs, the National Institute of Aging grants $2.8 million to Case Western Reserve University School of Medicine to identify potential FDA-approved medicines as repurposed agents for AD. The major classes of drugs investigated for AD as repurposed agents are antihypertensive, antidiabetic, antiasthmatic, retinoid receptors, anticancer agents, antiepileptic, antidepressive, and antimicrobial agents.[3] In addition to omics analysis, the concept of pharmacogenomics has gained significant attention in drug repurposing. Studies have suggested that drugs can regulate the expression of small noncoding RNAs such as micro RNAs (miRNAs) and their precursors. For instance, miravirsen is the first miRNA-targeted small molecule that has come in clinical trials and can inhibit miR-122 expression required to replicate hepatitis C virus.[4] In a study by Yu *et al.*, potential repurposing drugs were identified for breast cancer based on miRNA−disease−drug tripartite relationships.[5] Likewise, in a recent study, Aydin *et al.* reported miRNA-mediated repurposed drugs for Prolactinoma treatment *via in vitro* experimentation.[6]

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Drug repurposing is an opportunistic strategy of identifying new indications of the drugs already approved in the market. A review of different repurposing examples suggested that about 46 drugs have already been repurposed for various indications, and encouraging studies are consistently publishing.[7] A recent study has revealed that pharmaceutical companies have placed the market for repositioned drugs at $31.3 billion in 2020, generating about 25% of this industry's annual revenue. Recent estimates suggested that about 30% of the FDA-approved drugs are actually the repurposed drugs.[8]

To date, most of the repurposing studies have been published for parasitic diseases, multiple cancers, tuberculosis, and malaria.[9] This drug discovery strategy is gaining continuous appreciation as it bypasses the efforts and cost input required for the early stages of drug development. The repurposing of drugs involves two different approaches, computational and experimental.[10] Computational approaches are the combination of systematic steps taken for the initial identification of promising repurposable compounds. The primary methods used for the computational approach are network-based, text mining-based, and semantics-based.[11]

In the last few years, omics sciences accelerated the drug discovery process by overcoming the challenges associated with it. Recent technological advancements enabled scientists to develop genomics-, transcriptomics-, proteomics-, and metabolomics-based databases. Genomics studies helped us to understand the genetic basis of complex diseases.[12] In the past decade, the genome-wide association studies (GWAS) catalog has revolutionized the area of genomics to identify complex genotype−phenotype associations.[13] The transcriptomics studies help us to understand the effect of drugs on different cellular states. The expression profiling and genomics studies give the right directionality to gene−phenotype associations.[14,15] The proteomics studies are extensively used to understand the mechanistic basis of disease.[16] Similarly, the analysis of metabolome provides knowledge of associations of biochemical events with phenotypes.[17]

An exciting interplay between cancer and AD gives a direction to use anticancer drugs as repurposed therapeutics. Accumulating evidence has suggested that cancer and AD share some familiar biological hallmarks, and a significant link exists between cancer history and AD neuropathology.[18,19] In a recent study, Lee *et al.* established an interrelationship between cancer and AD at the transcription level. They compared differentially expressed genes between AD and nine different cancers and found that glioblastoma multiforme shared a strong correlation with AD.[20] The repurposing of oncology drugs for AD is underway, and many drugs, for instance, bosutinib, dasatinib, nilotinib, bexarotene, tamibarotene, and thalidomide (ClinicalTrials.gov identifier: NCT02921477, NCT04063124, NCT02947893, NCT01782742, NCT01120002, and NCT01094340, respectively), are in clinical trials for AD.[21] A study by Lonskaya *et al.* confirmed the therapeutic relevance of tyrosine kinase inhibitors nilotinib and bosutinib in AD, where the drugs facilitated amyloid clearance and reduced neuroinflammation.[22] A drug repurposing study by the neuroinformatics approach has proposed that the anticancer drug bexarotene could reduce Aβ aggregation by interacting with receptors for advanced glycation end products (RAGE) and beta-secretase (BACE-1).[23] A drug repurposing study by Madepalli Lakshmana and the group found that anticancer drug carmustine (BiCNU) could regulate amyloid precursor protein (APP) processing and trafficking to reduce Aβ aggregation in the brain.[24] Likewise, a study targeting vascular activation in AD has proposed that the anticancer drug sunitinib could reduce vascular activation of various proteins such as amyloid-beta, tumor necrosis factor-alpha (TNFα), interleukin-6 (IL-6), interleukin-1 beta, thrombin, and matrix metalloproteinase 9 and ameliorated cognitive dysfunction in AD transgenic mice. Additionally, a study on the antimitotic drug, paclitaxel, has revealed the drug's potential in reducing tau-associated pathologies by preventing tau-induced axonal swelling, reversal of microtubule polar orientation, prevention of neurite degeneration, and inhibition of impaired organelle transport and accumulation.[25] In parallel, a study on the tyrosine kinase inhibitor, pazopanib, in the AD mouse model has identified the potential of the drug in reducing tau pathology and astrocytic activity. The study has proposed that the drug could not alter microglial activity; however, it could modulate the activity of inflammatory markers and thus provide neuroprotection.[26]

The motivation of this study is to uncover the hidden neuroprotective potential of anticancer drugs. We adopted an integrated omics data-based repurposing strategy, including genomics, transcriptomics, and metabolomics, and validated our results by different computational methods. Our study was concentrated on FDA-approved anticancer drugs and their repurposing for AD. We developed a bioinformatic pipeline to assign a ranking of the repurposed drugs based on the computational drug repurposing score (CoDReS) validated by network and structural similarity analysis with approved AD drugs. The study also aims to combine the physicochemical analysis, drug-likeness, pathway analysis, and microRNA (miRNA) analysis of repurposing anticancer drugs to understand better the mechanisms involved. The study helped to identify the significant pathways and cancer-related genes associated with the pathogenesis of AD. The study also set a new direction to understand the complex relationship between AD and cancer that would be considered for other neurodegenerative diseases.

2. METHODOLOGY

2.1. Data Extraction. To obtain information on AD-associated genetic variations, we analyzed GWAS studies for AD from NHGRI-EBI GWAS catalog (http://www.ebi.ac.uk/gwas).[27] The database provides a consistent knowledge of single-nucleotide polymorphism (SNP)-trait associations for various diseases. We extracted GWAS data for (1) PUBMED ID, (2) study accession, (3) genes, (5) SNPs, (6) *P*-value, and (7) OR (odds ratio). Genes are considered significant, which fall under the genomic regions associated with SNPs ($r^2 > 0.6$). For transcriptomics data, NCBI Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) database that contains microarray and next-generation sequence functional genomic data sets was used.[28] The collected expression profile of the AD series GSE1297 was analyzed by GEO2R. The GSE1297 series contains microarray analysis data of the hippocampal region of 9 control and 22 AD subjects. The metabolomics data were collected from the Human Metabolome Database (HMDB, http://www.hmdb.ca), which contains 114,187 metabolite entries.[29] The database was searched for (1) AD linked metabolites, (2) protein name, (3) Uniprot ID, (4) type of metabolite, and (5) gene name.

2.2. Prioritization of Candidate Genes. We utilized two different computational tools to identify the most significant genes associated with AD. The genes obtained from various

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ACS Omega 2021, 6, 13870−13887

omics approaches were then subjected to enrichment analysis by online DAVID functional annotation tool and gene set to diseases (GS2D) tool. DAVID (https://david.ncifcrf.gov) provides an integrated platform to extract meaningful biological information from the list of genes enriched in genome-scale studies.[30] GS2D (http://cbdm.uni-mainz.de/geneset2diseases) is a web tool that performs enrichment analysis based on significant biomedical citations from PubMed.[31] The gene−disease associations were filtered by a minimum number of citations found (default = 5), the minimum number of gene−disease associations (default = 2), and the maximum false discovery rate (FDR = 0.05). The FDR is used as a matric in drug repurposing to measure significance of drug-indication scores.[32]

The enriched genes were then analyzed for protein−protein interaction (PPI) using the Molecular Interaction Search Tool (MIST) database. MIST (http://fgrtools.hms.harvard.edu/MIST/) database can be used to devise significant protein−protein and genetic interactions for different species.[33]

2.3. Drug Target Mapping. We have combined the information from genomics, transcriptomics, and metabolomics approaches and had a list of genes associated with AD. To develop a link between AD-related genes with currently available drug projects, we tracked two different databases. DrugBank (www.drugbank.com) (version 5.1.5) contains around 13,554 drug entries incorporating various approved and experimental small molecules and biologics.[34] Similarly, the Therapeutic Target Database (TTD) (http://db.idrblab.net/ttd/) accommodates 3419 targets and 37316 drug projects.[35] We included only those targets for which anticancer drugs are available and excluded the others. All the drugs with clinical, experimental, or withdrawn status were excluded, and only FDA-approved drugs were considered for this study. The information about drugs such as drug name, DrugBank ID, current indication, and drug mode of action was collected.

2.4. Validation of Candidate Drugs. The PPIs from the previous steps were then analyzed by the STRING database (string-db.org) that covers known and predicted interactions for different organisms.[36] The experimentally significant interactions (with high interaction scores) were selected, and the others were excluded from the study. The drug−target interactions were evaluated using the STITCH (search tool for interactions of chemicals) (http://stitch.embl.de/) database that integrates interactions of 300,000 chemicals and 2.6 million proteins.[37] In a complex system, two interacting genes are represented as nodes connected by an edge. The interaction networks were further analyzed, and networks were generated using Cytoscape software v3.3.0 (www.cytoscape.org).

For validation of promising drug candidates on the validation network, we measured network topology parameters such as degree centrality, betweenness, and topological coefficients using the CentiScaPe app on Cytoscape software. A degree is a topological parameter that corresponds to the number of interactions or connections for a given node. Betweenness corresponds to the centrality index of a given node. It represents the shortest path between two adjacent nodes. In biological networks, only a few nodes (hub nodes) have a high degree centrality and the nodes having the shortest path distance are designated as bottlenecks. Both hub nodes and bottlenecks are considered topologically important and biologically significant.[38] The topological coefficient is a relative measure that denotes the extent to which a node shares neighbors with other nodes in the network. The nodes that share no neighbor are assigned a topological coefficient value of 0. The candidate drugs were given ranks based on different topological parameters. The drugs having a higher degree centrality value were considered as topologically important and biologically significant. In short, the drugs (nodes) with higher degree centrality values are regarded as hub nodes with considerable importance in the network.

2.5. Drug Repurposing. The candidate drugs obtained from the previous studies were analyzed for their repurposing potential for AD using the CoDReS tool. CoDReS (http://bioinformatics.cing.ac.cy/codres) is a web-based tool that integrates information from the biologically available data sets, calculates affinity scores of protein and ligand pairs, and evaluates drug-likeness and structural similarities.[39] The candidate drugs with good repositioning scores were then presented by the hierarchical clustering algorithm of the ChemMine server.[40] Hierarchical clustering is a powerful approach to find structural and physicochemical similarities of compounds based on atom pair similarity measures. The similarity scores were calculated based on the *Z*-score values. Also, we calculated the structural similarity with the approved Alzheimer's drugs, namely, donepezil, rivastigmine, galantamine, and memantine. The similarity workbench tool of the ChemMine server was used, and similarity scores were represented as the Tanimoto coefficient, the most widely used metric to compare the molecular structure similarities in medicinal chemistry.[41] The tool utilizes the maximum common substructure (MCS) fingerprint method to find the largest substructures two compounds have in common and present it as the Tanimoto coefficient.

2.6. Literature Validation of the Drug−Disease Relationship. To obtain the information related to neuroprotective functions of anticancer drugs, we have searched the PubMed database using the keywords "anticancer drugs and neuroprotection," "anticancer drugs and AD," and anticancer drugs and neurodegenerative disorders. We collected information on whether the proposed repurposing drugs have any neuroprotective mechanism associated with them.

2.7. Swiss ADMET Analysis of Candidate Drugs. The development of drugs for the CNS disorders poses a challenge due to the blood−brain barrier (BBB). While designing a drug for brain diseases, physicochemical properties and brain permeation properties should be optimized. In consideration of this challenge, we analyzed our candidate repurposed drugs for physicochemical properties using the SwissADME analysis tool. SwissADME (http://www.swissadme.ch/) is a user-friendly web tool to predict physiochemical properties, pharmacokinetics, and drug-likeness of small molecules.[42] We collected information about physiochemical properties such as molecular weight, number of rotatable bonds, number of H-bond donor and acceptors present, partition coefficient (*M* log *P*), and topological polar surface area (TPSA) and blood−brain permeation, where *M* log *P* was the measure of lipophilicity and TPSA was the measure of the sum of the surfaces of polar atoms present.

2.8. Functional Similarity with MicroRNAs. To further validate our results, we identified miRNAs related to AD from Human microRNA Disease Database (HMDD) (https://www.cuilab.cn/hmdd).[43] HMDD contains information regarding experimentally validated microRNA−disease associations. We also retrieved information of miRNAs associated with the identified repurposed drugs and then constructed a network

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ACS Omega 2021, 6, 13870−13887

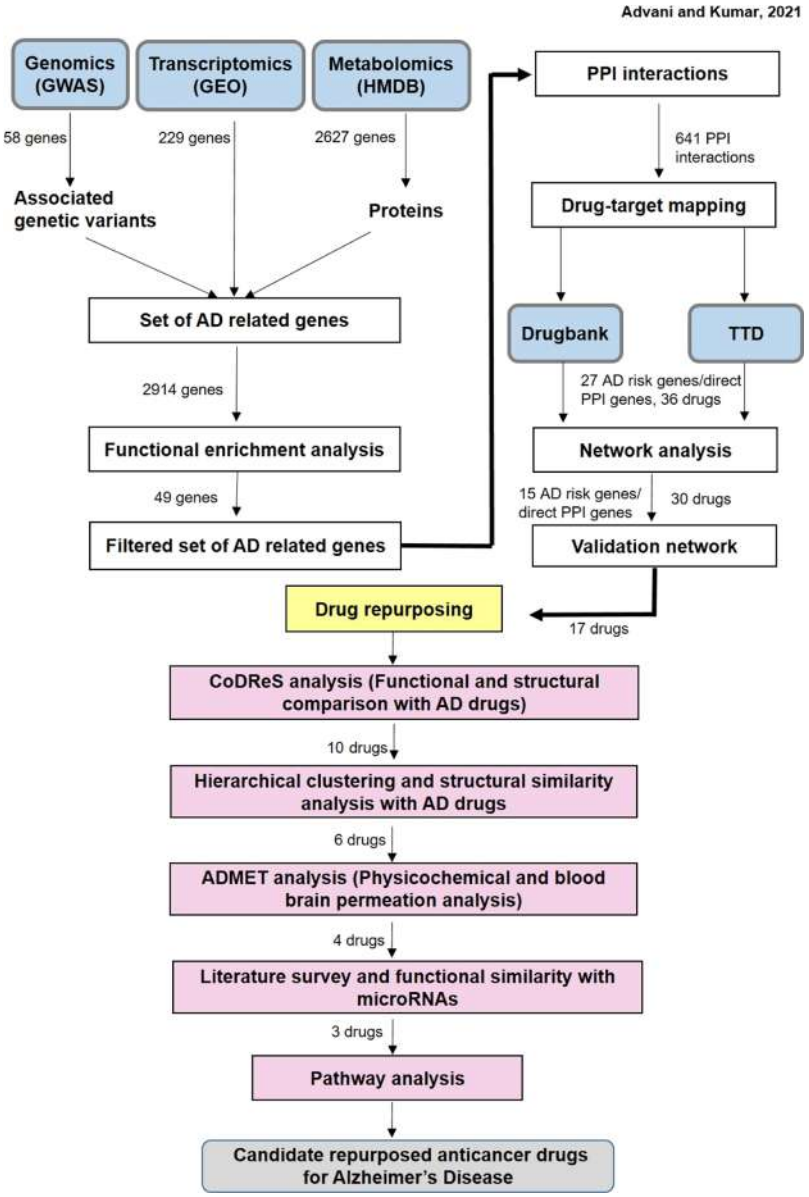

Figure 1. Flow chart of drug repurposing by omics data mining: We retrieved information on AD risk genes from GWAS, transcriptomics, and metabolomics approaches. We found 2914 AD risk genes from which 58 genes were extracted from GWAS, 229 genes were extracted from GEO transcriptomics data, and 2627 genes were related to 128 metabolites from the HMDB database. After functional enrichment analysis, we filtered out 49 AD-associated targets. The PPI network analysis resulted in 641 PPI interactions. We performed drug target mapping to find candidate drugs from DrugBank and TTD databases. Out of 641, 25 PPI interactions were found to be associated with 36 approved anticancer drugs. We excluded the information related to investigational and experimental drugs. We analyzed gene−gene and gene−drug interactions and selected the top 10 PPI interactions that correspond to 30 anticancer compounds. These 30 drugs were then analyzed by the CoDReS web tool that proposes 10 candidate drugs for AD. These drugs were then compared with the available Alzheimer's therapeutics for structural and functional similarities, where six drugs have shown to be hierarchically clustered. ADMET analysis, pathway analysis, and functional similarity with miRNAs resulted in potential repurposing anticancer drugs against AD.

that combines miRNAs that share common targets between the repurposed drugs and AD. We considered only the miRNAs that were neuroprotective in nature. The disease−miRNA−drug and miRNA−drug relationships were presented in the form of a network using Cytoscape software. The information of AD-related miRNAs, repurposed drugs, and their targets was given as the input.

2.9. Pathway Analysis. To establish a connection of AD-related genes with cancer, we compare the expression pattern of genes with AD and the most common 13 types of cancers prescribed by the National Cancer Institute (NIH).[44] To discover the molecular mechanisms regulated by the identified genes, we performed pathway analysis (KEGG,[45] Bioplanet,[46] and WikiPathways[47]) using the Enrichr tool. Enrichr (http://amp.pharm.mssm.edu/Enrichr/) is a web-based enrichment analysis tool that accumulates biological knowledge (genes, diseases, pathways, and drugs) of more than 102 gene set libraries.[48] The tool has provided information about biologically relevant pathways or enriched pathways for the set of the given genes. These enriched pathways were associated with the given gene list more than would be expected by chance. We also extracted the information of disease signatures

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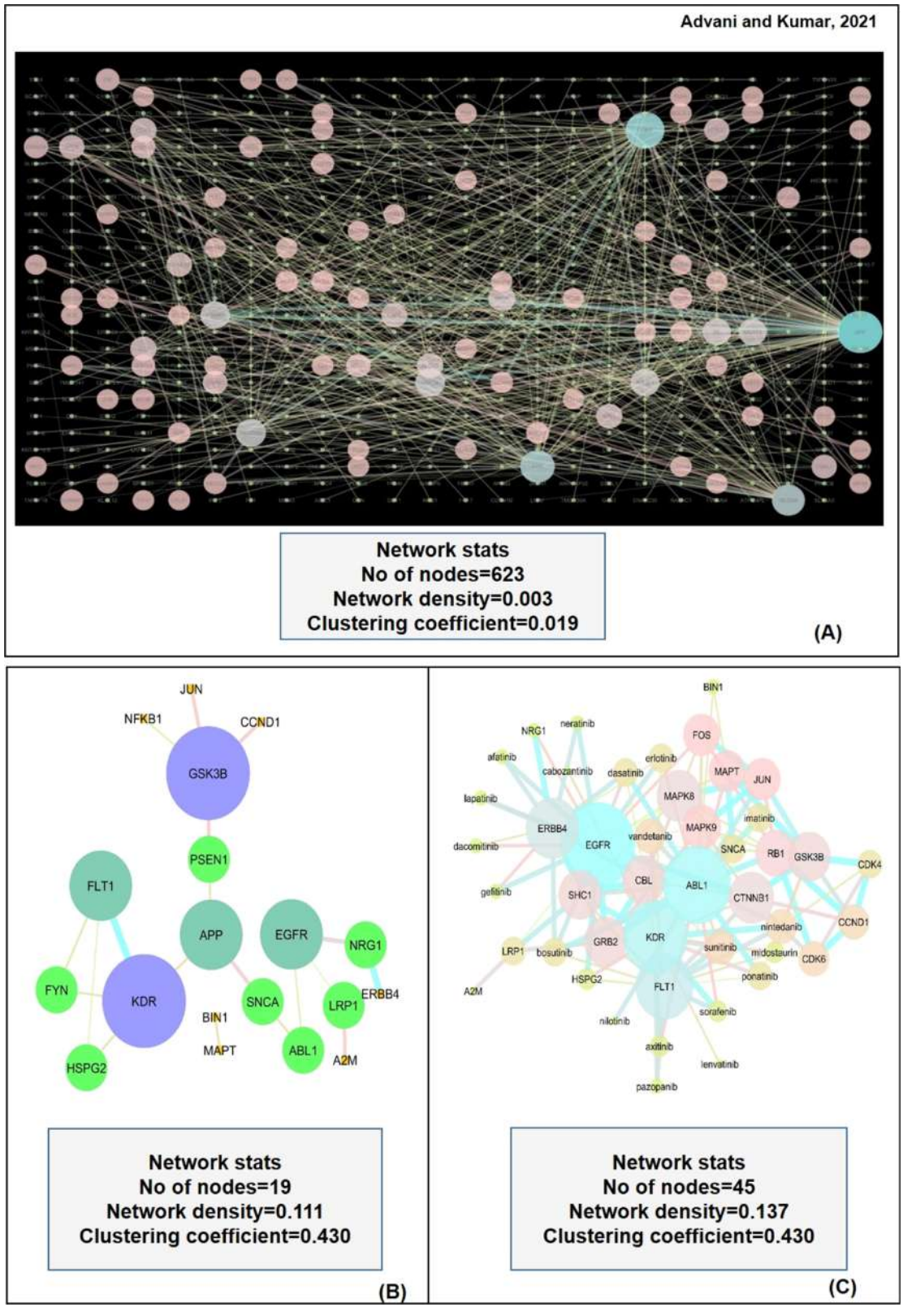

Figure 2. (A) Network is showing PPI interactions for AD-related genes. (B) STRING network of experimentally significant interactions. Glycogen synthase kinase 3 beta (GSK3B), vascular endothelial growth factor receptor 2 (KDR), APP, vascular endothelial growth factor receptor 1 (FLT1), and epidermal growth factor receptor (EGFR) were identified as the hub nodes. (C) STITCH network of drug-gene interactions. Nintedanib, sunitinib, vandetanib, dasatinib, erlotinib, imatinib, ponatinib, and bosutinib were reported as hub nodes as drugs. The size of individual nodes and the thickness of edges correspond to the significance and strength of interactions, respectively.

(DisGeNET and OMIM-based information) related to the given genes using the Enrichr tool. The output of Enrichr is ranked list terms, and ranking is provided based on *p*-value scores. Enrichr calculates the *p*-value based on Fisher's exact

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ACS Omega 2021, 6, 13870−13887

test that assumes binomial distribution and independence for the probability of the given input gene.

An overview of the complete pipeline is shown in Figure 1.

3. RESULTS

3.1. Omics Data Mining and Enrichment Analysis Revealed AD-Related Genes. The omics data approach enabled us to identify AD-related genes. We collected information about 58 unique genes from 37 GWAS studies. The *P*-value of the identified genes varies from 8×10^{-189} (minimum) to 8×10^{-6} (maximum). We identified 229 genes in the form of differentially coexpressed genes from transcriptomics studies. The data obtained from the HMDB database reported 128 AD-related metabolites that correspond to 2627 genes from metabolomics data. Most of the proteins associated with the retrieved metabolites had unknown functions, while some were enzymes or transporters. We combined the information from different omics approaches, and finally, 2914 genes were found to be associated with AD.

DAVID functional enrichment analysis of 2914 genes revealed that 13 genes from GWAS studies, 18 genes from the transcriptomics approach, and 239 genes from the metabolomics approach have significant associations with AD. Similarly, GS2D functional enrichment analysis revealed that 12 genes from GWAS studies, 4 genes from the transcriptomics approach, and 62 genes from the metabolomics approach were significantly linked with AD.

When we compared the two enrichment analysis methods, 49 AD-related genes were shared in the two enrichment methods (Table S1).

3.2. PPI Network Analysis Revealed Potential Interactors of AD-Risk Genes. We evaluated the PPI network of the 49 AD-risk genes to explore the possibility of any of the genes from the PPI network that serve as a target for approved anticancer drugs. We selected PPI interactions with a high confidence score and excluded the interactions with medium to low confidence. We found 641 PPI interactions from the MIST database results, as shown in Figure 2A. All the PPI genes of 641 interactions, along with 49 AD-risk genes, were searched in the DrugBank database and TTD to find the association with known anticancer drugs. Among the PPI interactors, 17 genes were reported to have approved anticancer medications available in the considered drug repositories. We found that the epidermal growth receptor (EGFR) is the most frequently appeared PPI interactor interacting with four different AD-associated targets APP, alpha-synuclein (SNCA), neuregulin 1 (NRG1), and LDL receptor related protein 1 (LRP1). These PPI interactions were then evaluated by the STRING database and presented on the validation network, as shown in Figure 2B. The topological parameters of genes in STRING, such as degree centrality, betweenness, and topological coefficients, were analyzed by Cytoscape and are presented in Table 1.

The topological parameters were used to identify the hub nodes in the validation network. We identified glycogen synthase kinase beta (GSK3B), kinase insert domain receptor (KDR), APP, EGFR, and Fms-related receptor tyrosine kinase 1 (FLT1) as the top five nodes. GSK3B and KDR had the highest degree centrality values of 4.0 and betweenness values of 0.35 and 0.32, respectively, while APP, EGFR, and FLT1 had degree centrality values of 4 and betweenness values of 0.69, 0.43, and 0.004, respectively. Among the identified genes, GSK3B is a multifunctional protein kinase regulating various cellular processes and is implicated in several diseases. In AD,

Table 1. Topological Parameters of Genes (Nodes) on the STRING Validation Network Using CentiScaPe App on Cytoscape Software[a]

Gene	Degree	Betweenness	Topological Coefficient
GSK3B	4	0.35	0.25
KDR	4	0.329166667	0.45
APP	3	0.691666667	0.333333333
EGFR	3	0.433333333	0.333333333
FLT1	3	0.004166667	0.666666667
SNCA	2	0.5	0.5
ABL1	2	0.458333333	0.5
PSEN1	2	0.4	0.5
NRG1	2	0.125	0.5
LRP1	2	0.125	0.5
HSPG2	2	0	0.875
FYN	2	0	0.875
ERBB4	1	0	0
JUN	1	0	0
CCND1	1	0	0
A2M	1	0	0
MAPT	1	0	0
BIN1	1	0	0
NFKB1	1	0	0

[a]Genes with significant values are highlighted.

GSK3 is considered a regulator of the two pathological hallmarks, senile plaques and neurofibrillary tangles.[49,50] The other identified target APP is a single transmembrane protein that acts as a multifunctional cell surface receptor. APP plays a major role in AD pathogenesis as it is associated with Aβ production, synaptic function, and neuronal homeostasis.[51,52] The EGFR is a transmembrane molecule that belongs to the HER/ERBb superfamily of receptors. The binding of ligands to this receptor triggers several signaling pathways that promote cell proliferation and cell survival. The other two genes, vascular endothelial growth factor receptor (VEGFR1) or FLT1 and VEGFR2 or KDR, are the two receptors playing a significant role in the signal transduction pathways mediated by the VEGF.[53] Some studies have suggested that both FLT1 and KDR are associated with AD neuropathology by inhibiting pro-angiogenic signaling mediated by the VEGF.[54,55]

3.3. Drug Mapping Identified Potential Repurposing Candidates for AD. Drug target mapping from DrugBank and TTD has shown that 28 direct PPI/AD risk genes were associated with 36 FDA-approved anticancer drugs (Table S2). We omitted the targets related to any investigational, experimental, or withdrawn anticancer drugs. From 36 drugs, 11 drugs were associated with only one direct PPI gene/AD risk gene, while 25 drugs were those that interacted with more than one gene. The retrieved drugs were related to diverse modes of actions, such as inhibitors, antagonists, substrates, and some had unknown functions. The experimentally significant interactions obtained from STRING analysis corresponded to 30 drugs from which 4 drugs (brigatinib, zanubrutinib, osimertinib, and erdafitinib) were not identified by the STITCH database and were excluded from the study.

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Of the 26 candidate repurposing drugs, six drugs (cisplatin, encorafenib, vinblastine, paclitaxel, docetaxel, and regorafenib) had not shown any interaction.

Additionally, three drugs (bosutinib, nilotinib, and dasatinib) were in clinical trials for AD or related dementias and were not included in this study. Therefore, the remaining 17 drugs were considered novel candidate repurposing drugs for AD. The candidate drugs with their AD-related targets and PPI targets are summarized in Figure 3.

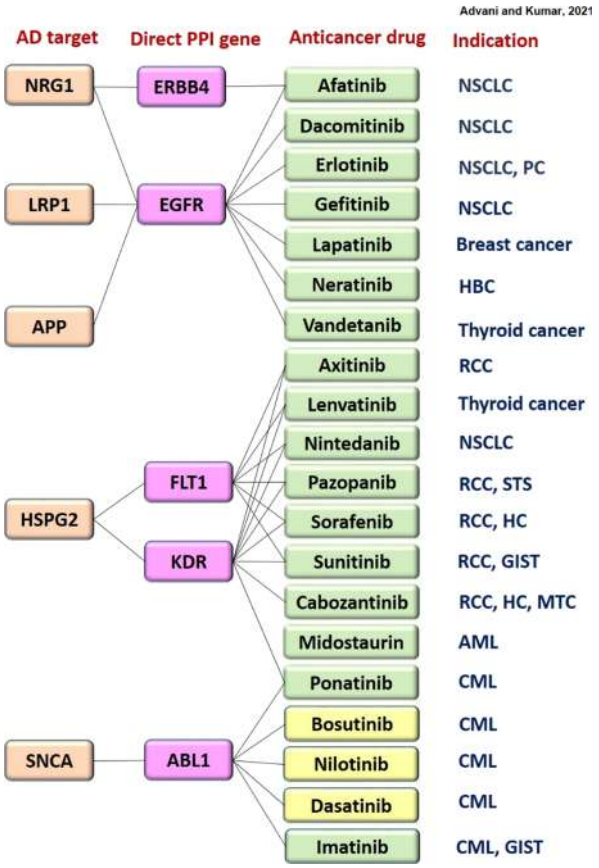

Figure 3. Summary of AD risk genes, genes in direct PPI, and targeted anticancer drugs. Drugs shown in yellow boxes were known in clinical studies as AD therapeutics, and drugs in green boxes were considered as potential repurposing candidates. Some drugs such as afatinib, axitinib, lenvatinib, nintedanib, pazopanib, sorafenib, and ponatinib interact with more than one target. NRG1: neuregulin 1; ERBB4: Erb-B2 receptor tyrosine kinase 4; LRP1: LDL receptor-related protein 1; EGFR: epidermal growth factor receptor; HSPG2: heparan sulfate proteoglycan 2; FLT1: Fms-related receptor tyrosine kinase 1; KDR: kinase insert domain receptor; SNCA: synuclein alpha; ABL1: ABL proto-oncogene 1, nonreceptor tyrosine kinase, NSCLC: nonsmall cell lung cancer, PC: pancreatic cancer, HBC: HER-positive breast cancer, RCC: renal cell carcinoma, STS: soft-tissue sarcoma, HC: hepatocellular carcinoma, GIST: gastrointestinal tumors, MTC: medullary thyroid cancer, AML: acute myelogenous leukemia, and CML: chronic myelogenous leukemia.

3.4. Computational Validation of Candidate Repurposed Drugs. The drug-gene validation network was constructed using the STITCH database (Figure 2C) and analyzed using Cytoscape software, and drugs were ranked based on the degree centrality and betweenness values. The results shown in Table 2 have indicated that the known anticancer drugs, dasatinib and bosutinib, were the hub nodes among known neuroprotective anticancer drugs with the highest value of degree centrality of 4.0 and betweenness values of 0.007 and 0.004, respectively. Similarly, nintedanib, sunitinib, and vandetanib were identified as the important hub nodes among promising drug candidates with a degree centrality of 5.0 and betweenness values of 0.026, 0.021, and 0.011, respectively. We also identified the interactive targets of the topologically important drugs. The most considerable node nintedanib had a strong relationship with the genes KDR, FLT1, GSK3B, cyclin-dependent kinase 4 (CDK4), and ABL proto-oncogene 1 (ABL1). Similarly, sunitinib interacted on the validation network with FLT1, KDR, EGFR, CDK6, and ABL1, while vandetanib had close interactions with ABL1, EGFR, KDR, and FLT1.

3.5. Functional and Structural Analysis Validated the Repurposing Potential of Candidate Drugs. The potential repurposing candidates from the previous steps were evaluated for their functional and structural properties by the CoDReS tool. The tool is based on a disease-specific approach to compare drug−disease relationships concerning a training set of drugs approved or investigated for a disease. We have incorporated this tool to rerank the candidate drugs based on their repurposing scores. The comparative values for different drugs have been provided in (Table S3). Figure 4A−C has illustrated the comparative functional, structural, and CoDReS scores of the candidate drugs, respectively. The values have suggested that most of the drugs have good structural scores, but functional scores have shown significant variations. We found that erlotinib had the highest functional score (1.0), while dacomitinib had the lowest value (0.001). Similarly, sunitinib, sorafenib, imatinib, gefitinib, vandetanib, lenvatinib, pazopanib, axitinib, afatinib, and dacomitinib had the highest values (1.0) in terms of structural score, and lapatinib had the lowest score (0.33). Moreover, erlotinib had the highest CoDReS value (1.0), and lapatinib had the lowest value (0.20). We have selected the top 10 drugs with the highest CoDReS scores for further study. The CoDReS results have indicated that erlotinib would be a good repurposing drug having the highest functional and structural scores.

Additionally, we exploited the ChemMine server to investigate anti-Alzheimer's properties of candidate drugs and compared their clinical potential with donepezil, rivastigmine, galantamine, and memantine. The hierarchical clustering was performed using a clustering threshold of 1. We noticed no drug clusters with typical anti-Alzheimer drugs. We have selected the closest neighbors to Donepezil such as vandetanib, gefitinib, erlotinib, imatinib, afatinib, and sunitinib. Similarly, for another anti-Alzheimer drug rivastigmine, we found sunitinib as the closest match. Likewise, for galantamine, we found vandetanib, erlotinib, and gefitinib as the closest neighbors. We have found no nearest neighbor to memantine. The results are presented in Table 3. The best candidates obtained from clustering analysis have also demonstrated good structural similarity values, as highlighted in red in the table. Finally, we have selected 6 out of 10 drugs for supplementary analysis. The clustered groups were represented in the form of a heat map, as shown in Figure 4D.

3.6. Literature Studies and ADMET Analysis Evaluated the Neuroprotective Potential of Repurposed Drugs. To further validate our results, we have searched for the available information regarding the neuroprotective properties of the drugs proposed from the previous steps. A few bibliographic studies were available regarding neuro-

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Table 2. Topological Parameters of Drugs on the Validation Network[a]

Rank	Drug name	Degree	Betweenness	Topological Coefficient
1	Nintedanib	5	0.026	0.44
2	Sunitinib	5	0.021	0.402
3	Vandetanib	5	0.011	0.482
4	Dasatinib	4	0.007	0.502
5	Erlotinib	4	0.007	0.502
5	Imatinib	4	0.006	0.548
6	Ponatinib	4	0.006	0.543
6	Bosutinib	4	0.004	0.513
7	Axitinib	3	0.002	0.679
7	Sorafenib	3	0.002	0.679
7	Midostaurin	3	0.002	0.597
8	Pazopanib	2	0	0.875
8	Afatinib	2	0	0.791
8	Dacomitinib	2	0	0.791
8	Gefitinib	2	0	0.791
8	Lapatinib	2	0	0.791
8	Neratinib	2	0	0.791
9	Cabozantinib	1	0	0
9	Lenvatinib	1	0	0
9	Nilotinib	1	0	0

[a]Promising drugs with the highest ranks are highlighted in pink, and known neuroprotective anticancer drugs are highlighted in green.

protective functions of anticancer drugs, as summarized in Table 4. Based on these results, we confirmed that all six drugs have repurposing potential for AD. ADMET analysis of the six drugs has confirmed that four drugs (erlotinib, gefitinib, vandetanib, and sunitinib) have good physicochemical properties (molecular weight, no of rotatable bonds, no of H-bond donors, no of H-bond acceptors, TPSA, and M log P) and were able to cross the BBB, as shown in (Table S4). Two drugs, afatinib and imatinib, would not be able to cross the BBB and thus were excluded from the study.

3.7. Functional Similarity Analysis with MicroRNAs. To further validate our results, we extracted the list of AD-related miRNAs and also searched for the miRNAs related to the repurposed drugs (Table S5). After comparison, we found that erlotinib and gefitinib shared three miRNAs with AD where only one miRNA has neuroprotective functions, while vandetanib shared 33 different miRNAs with AD, as shown in the network in Figure 5. Of the 33 miRNAs, 11 miRNAs have neuroprotective functions. We found that miRNA-200a is the only AD-related miRNA with a neuroprotective function associated with all three drugs. miRNA-200a targets the EGFR gene, and a literature survey has confirmed its neuroprotective role in attenuating amyloid-beta overproduction by down-regulating BACE1 expression and tau hyperphosphorylation by reducing the expression of protein kinase A (PKA).[65]

3.8. Pathway Analysis Confirmed the Repurposing Potential of EGFR Inhibitors. The significant AD-related genes were searched in the DisGeNET database to develop an expression pattern among AD and various types of cancers. The results are presented in the form of a heat map shown in Table 5 where the blue color represents high expression values, while the red color represents low expression values. We found that CCND1, EGFR, and KDR are among the top genes which are commonly expressed in AD and in a different type of cancer. Furthermore, the experimentally significant gene interactions obtained from the STRING database were considered for pathway analysis by the Enrichr tool. We used KEGG, BioPlanet, and WikiPathway databases for pathway analysis (Table 6).

The most frequently appeared genes in the enriched pathways (biologically relevant) were the EGFR, JUN, and GSK3B. The ERBb signaling pathway, focal adhesion, mitogen-activated protein kinase (MAPK) signaling, Cu homeostasis, and phosphatidylinositol-3-kinase (PI3-Akt) pathways were the top signaling pathways associated with AD pathogenesis. There were many pieces of evidence available for the pathways identified by our study with AD. The pathological role of ErBb4 activity in AD is confirmed by Woo *et al.*, where ErBb4 was accompanied by AD progression.[66] The role of focal adhesion signaling in AD pathology is established because Aβ upregulates many proteins related to focal adhesion signaling that induce re-entry of neurons into the cell cycle.[67] Aberrant activation of focal adhesion kinases is associated with synaptic loss and neuronal dystrophy in AD.[68] Many studies have proposed that MAPK signaling plays an essential role in AD pathogenesis by regulating tau phosphorylation, APP processing, and neuronal apoptosis.[69] Several MAPKs interact with AD-related proteins such as tau, APP, presenilin (PS), and apolipoprotein E (ApoE).[70] The role of Cu in AD pathogenesis is controversial. Some studies have demonstrated that Cu overload is responsible for neurotoxicity in AD brains, while other studies

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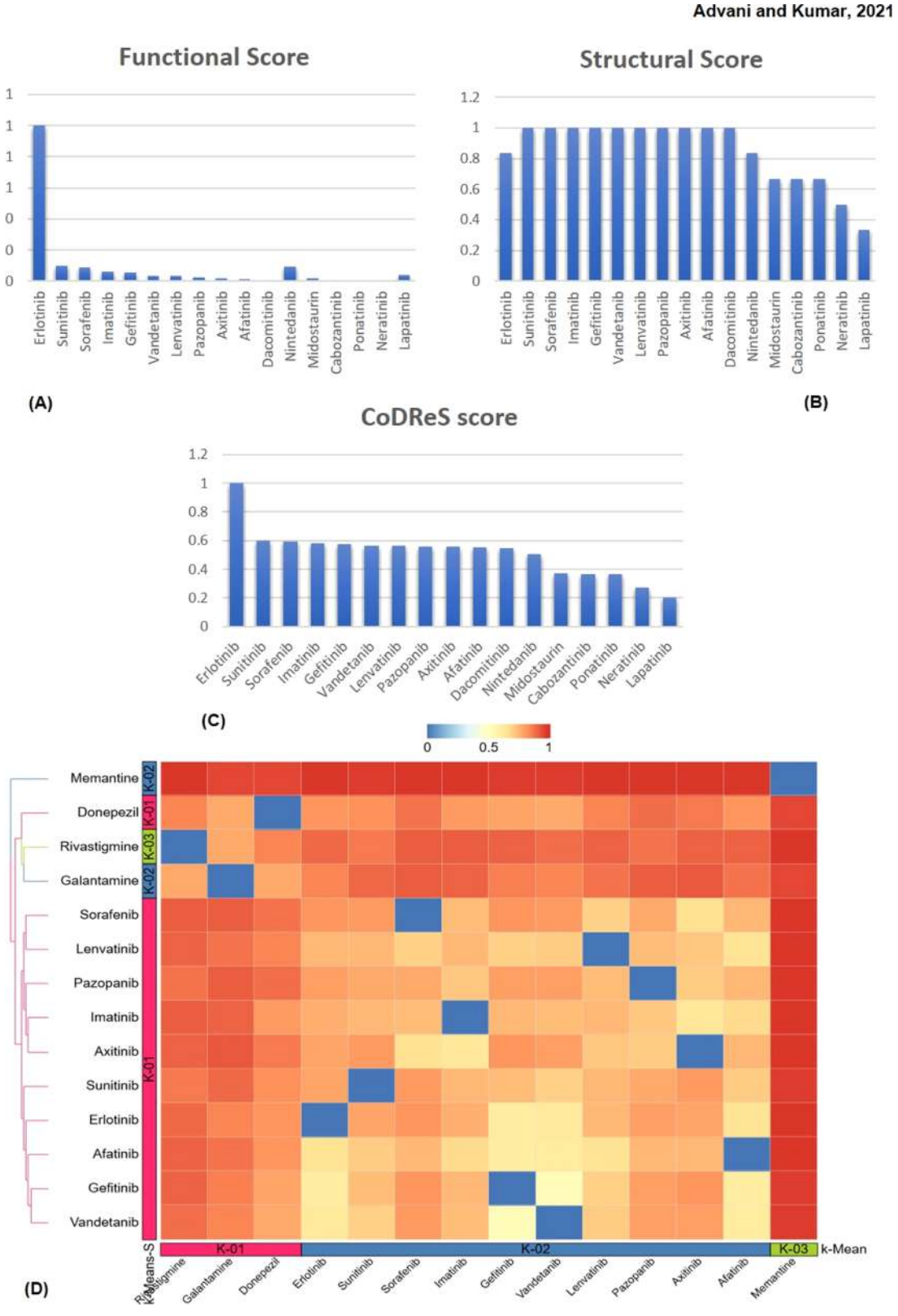

Figure 4. (A) Functional scores of different candidate repurposing drugs as calculated using the CoDReS tool. (B) Structural scores of different candidate repurposing drugs as calculated using the CoDReS tool. (C) CoDReS scores of candidate repurposing drugs. Erlotinib is shown as the most promising repurposing drug with good structural and functional scores. The structural scores of the drugs are more or less similar, while the functional scores have shown great variations. (D) Clustered heat map of candidate repurposing drugs with known Alzheimer's drugs donepezil, rivastigmine, galantamine, and memantine. The heat map is generated using a distance matrix as the input generated by subtracting the similarity coefficient from 1. The colors from blue to red represent the correlation intensities of drugs where blue represents complete correlation and red represents no correlation.

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ACS Omega 2021, 6, 13870−13887

Table 3. Similarity Scores (Tanimoto Coefficient) of Repurposed Drugs with Known Alzheimer's Drugs[a]

Drug	Donepezil	Rivastigmine	Galantamine	Memantine
Afatinib	0.176	0.086	0.112	0.009
Axitinib	0.128	0.081	0.067	0
Erlotinib	0.175	0.096	0.147	0.004
Gefitinib	0.207	0.084	0.138	0.014
Imatinib	0.182	0.076	0.881	0.008
Lenvatinib	0.149	0.086	0.112	0.003
Pazopanib	0.104	0.119	0.076	0.001
Sorafenib	0.119	0.070	0.072	0
Sunitinib	0.166	0.129	0.100	0.012
Vandetanib	0.218	0.105	0.149	0.017

[a]Highlighted drugs have more or less similar scores to known AD drugs.

Table 4. Literature Studies for Neuroprotective Functions of Potential Repurposing Candidates

drug	neuroprotective function	references
afatinib	inhibition of oxygen/glucose-induced neuroinflammation and EGFR activation	56
erlotinib	reduction in Aβ-induced memory loss in AD	57
gefitinib	improvement in cognition and memory functions	57
	may improve AD pathogenesis by inhibiting the β-secretase activity	58
imatinib	inhibition of Aβ accumulation by the selective inhibition of BACE activity	59
	promotes degradation of Aβ by inducing the activity of Aβ-degrading enzyme neprilysin	60
	inhibition of brain c-Abl, reduction in circulating levels of Aβ, shifts APP processing to non-amyloidogenic pathway	61
sunitinib	provides neuroprotection by inhibiting NO production	62
	inhibition of acetylcholinesterase activity and attenuation of cognitive impairments in scopolamine-induced AD mice	63
vandetanib	may inhibit acetylcholinesterase activity in AD	64

have proposed Cu deficiency as a contributing factor to AD pathogenesis.[71] Likewise, the role of the PI3K pathway is confirmed by studies where abnormal activities of the pathway were responsible for Aβ production and sequestration.[72] The PI3K pathway activation has therapeutic potential to treat AD as some of the drugs such as donepezil, coenzyme Q10, and human telomerase reverse transcriptase (hTERT) are known to treat AD by GSK3B inhibition and PI3K activation.[73]

DisGeNET and OMIM databases were used to find the most closely associated diseases with the identified genes (Table 7). The DisGeNET results reported that out of 15 genes, 13 genes were associated with AD (P-value 7.44×10^{-12}), while OMIM disease analysis identified 3 genes (P-value 5.77×10^{-5}) related to AD. Functional classification of identified genes from STRING interactions and their associated drugs retrieved from the STITCH network has revealed that kinases and their inhibitors are the major class of targets and targeted drugs associated with AD, respectively (Figure 6).

4. DISCUSSION

Drug repurposing is a productive approach to identify novel therapeutic uses of available drugs. The common biological pathways of different diseases and the advancements in system biology tools open up new horizons to analyze the off-target effects of approved drugs for various indications. Over the last decade, several studies have been published, emphasizing the shared molecular mechanism of cancer and AD. Indeed, drug repurposing of anticancer drugs as neuroprotective agents has been applied to overcome AD-related clinical consequences. However, the complexity of different neuropathological states and limited understanding of different cellular signaling mechanisms in AD posed a big challenge to develop repurpose therapeutics. In the present study, we used an integrated approach to reveal potential AD-related targets. We opted for a comprehensive data analysis approach to identify neuroprotective anticancer drugs and analyzed the data with network-based and pathway-based tools. We identified 49 AD-related genes by combining GWAS, transcriptomics, and metabolomics studies. We reported 17 cancer-related genes that have direct interactions with the identified AD-related targets. We identified 36 approved anticancer drugs that have associations with these targeting genes. For further study, we selected the experimentally significant genes with the highest interaction scores, as shown in the STRING network. We found 30 anticancer drugs as respective targets of the experimentally significant genes.

Computational validation by CoDReS ranked the repurposing drugs based on their functional and structural properties. Among the proposed drugs, dasatinib (phase I/II), nilotinib (phase II), and bosutinib (phase I) are in clinical trials as repurposed therapeutics for AD, thus validating the authenticity of our drug repurposing approach. The top 10 drugs obtained from CoDReS scoring were analyzed for their similarities with the known AD drugs and clustered based on their similarity scores. We selected the closest neighbors, vandetanib, erlotinib, gefitinib, afatinib, imatinib, and sunitinib. The literature studies have confirmed the repurposing potential of these anticancer drugs. The ADMET analysis of these six drugs revealed that afatinib and imatinib did not possess good physicochemical properties and were not BBB-penetrant. Thus, we proposed vandetanib, erlotinib, gefitinib, and sunitinib as potential repurposing drugs.

The pathway analysis identified the EGFR and GSK3B as the most frequently appeared genes in AD-associated pathways. The CCND1, EGFR, and KDR are found as the most commonly expressed genes in AD and in 13 most common types of cancers. Network analysis of PPI interactions revealed that GSK3B, KDR, APP, EGFR, and FLT1 were the hub genes

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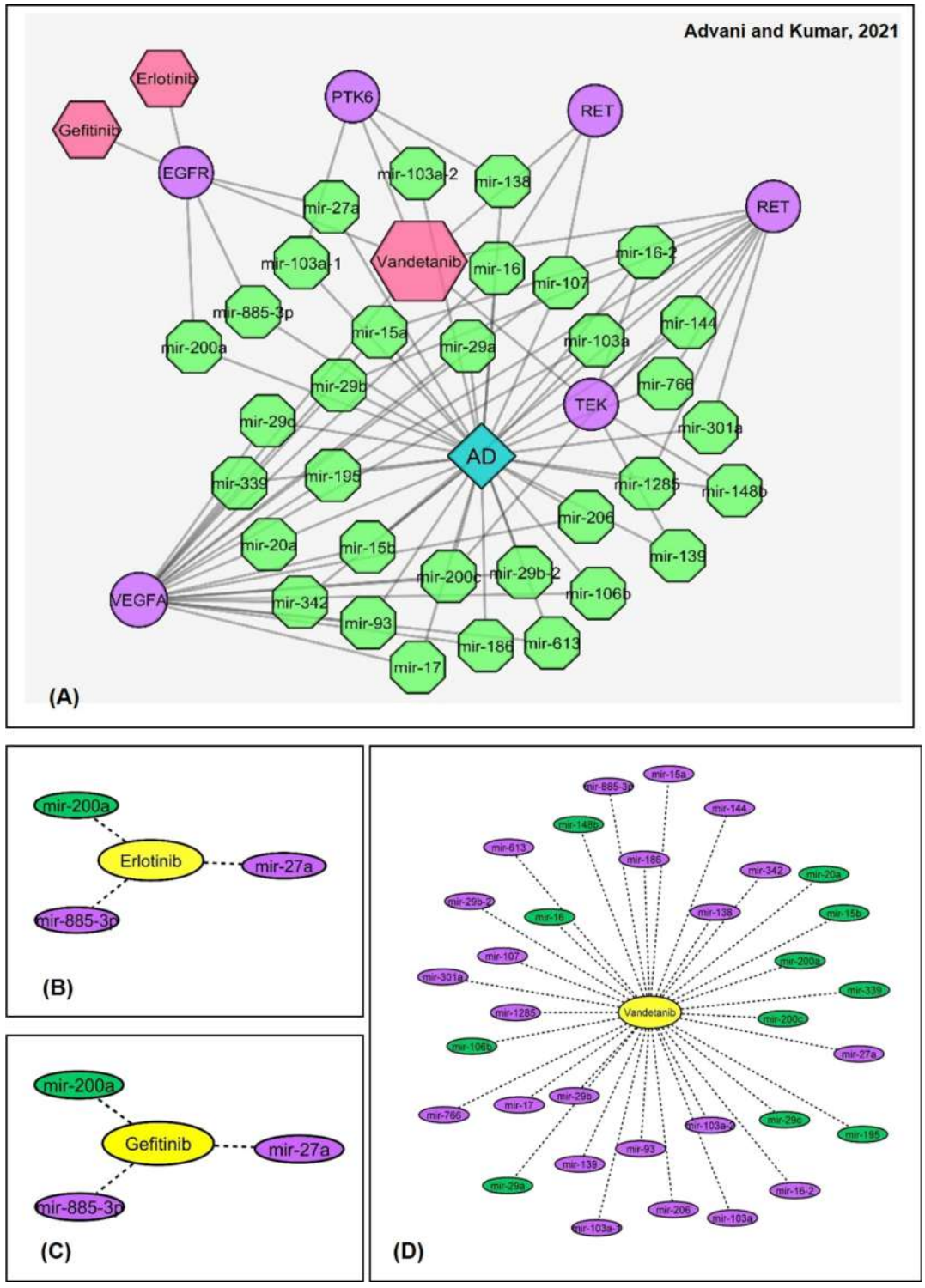

Figure 5. (A) Network is showing the interrelationship of miRNAs associated with AD and those associated with repurposed anticancer drugs erlotinib, gefitinib, and vandetanib. The network shows that vandetanib shares many common targets such as EGFR, PTK6, RET, TEK, and VEGFA with AD-related miRNAs, while both erlotinib and gefitinib share functional similarity through the EGFR gene. (B−D) Association of erlotinib, gefitinb, and vandetanib with miRNAs, respectively, where miRNAs shown in green are neuroprotective, while miRNAs shown in purple are neurodegenerative as identified through literature analysis. miRNA-200a is the only one that shows association with all three repurposed drugs.

in the PPI network. Literature studies have supported the neuroprotective potential of these targets and their associated drugs. In short, our integrated omics analysis with computational validation tools had prioritized the role of GSK3B and EGFR in AD pathogenesis. ErBb signaling, focal adhesion, MAPK pathway, Cu homeostasis, and PI3-Akt were the over-representative pathways targeted by these genes that we prioritized by pathway analysis using different databases. However, the therapeutic relevance of targeting the EGFR in AD is not well established. Still, some studies have supported the fact that the EGFR prevents Aβ and ApoE-induced cognitive deficits and considered a preferred target for treating

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Table 5. Heat Map Showing the Expression Pattern of Shared Genes between AD and 13 Most Common Cancer Types[a]

	ABL1	A2M	BIN1	CCND1	ERBB4	EGFR	FLT1	GSK3B	HSPG2	JUN	KDR	LRP1	MAPT	NRG1	SNCA
AD															
Bladder cancer															
Breast cancer															
Colorectal cancer															
Endometrial cancer															
Kidney cancer															
Leukemia															
Liver cancer															
Lung cancer															
Melanoma															
NHL															
Pancreatic cancer															
Prostatic cancer															
Thyroid cancer															

[a]AD: Alzheimer's disease; NHL: non-Hodgkin lymphoma.

Table 6. Pathway Analysis of STRING Interactions Based on *p*-Values[a]

S.No.	Pathway name	Genes involved	P-value[bb]
KEGG pathway analysis			
1	ErBb signaling pathway	GSK3B,JUN,ERBB4,ABL1,NRG1,EGFR	2.39E-11
2	Focal adhesion	GSK3B,JUN,FLT1,CCND1,KDR,EGFR	4.18E-11
3	MAPK signaling pathway	MAPT,JUN,FLT1,ERBB4,KDR,EGFR	4.38E-11
BioPlanet pathway analysis			
1	ErBb signaling pathway	GSK3B, JUN, CCND1, ERBB4, ABL1, NRG1,EGFR	2.52E-13
2	Focal adhesion	GSK3B, JUN, CCND1, FLT1, KDR, EGFR	1.08E-08
3	PI3-Akt pathway	GSK3B, ERBB4, NRG1, EGFR	2.73E-08
WikiPathway analysis			
1	ErBb signaling pathway	GSK3B, JUN, CCND1, ERBB4, ABL1, NRG1,EGFR	1.99E-13
2	Cu homeostasis	APP, GSK3B, JUN, CCND1, MAPT	2.87E-10
3	Focal adhesion	JUN, GSK3B, FLT1, CCND1, KDR, EGFR	4.06E-09

[a]Genes in red are the most frequently appeared genes in the enriched pathways. [b]Here, the *p*-value represents the probability of any gene belonging to a biological pathway.

Table 7. Disease-Based Analysis of STRING Interactions Based on *p*-Values

S.No.	Disease name	Genes involved	P-value[a]
DisGeNET analysis			
1	Amyloidosis	APP,BIN1,EGFR,ERBB4,FLT1,GSK3B,HSPG2,LRP1,MAPT,NRG1,SNCA	7.19E-13
2	Melanoma	ABL1,APP,BIN1,CCND1,EGFR,ERBB4,FLT1,GSK3B,HSPG2,JUN,KDR,LRP1,NRG1,SNCA	2.26E-12
3	Alzheimer's Disease	ABL1,APP,BIN1,CCND1,EGFR,ERBB4,GSK3B,HSPG2,JUN,LRP1,MAPT,NRG1,SNCA	7.44E-12
4	Central Neuroblastoma	APP,BIN1,CCND1,EGFR,ERBB4,FLT1,GSK3B,JUN,KDR,LRP1,MAPT,SNCA	3.57E-11
5	Non-small cancer lung carcinoma	ABL1,APP,BIN1,CCND1,EGFR,ERBB4,FLT1,GSK3B,JUN,KDR,LRP1,NRG1,SNCA	3.63E-11
OMIM disease analysis			
1	Dementia	APP,CCND1,EGFR,MAPT,SNCA	4.52E-09
2	Parkinson's Disease	CCND1,EGFR, MAPT,SNCA	7.39E-07
3	Alzheimer's Disease	APP, CCND1, EGFR	5.77E-05
4	Schizophrenia	CCND1,EGFR,NRG1	6.46E-05
5	Myopathy	BIN1,CCND1, EGFR	9.09E-05

[a]Here, the *p*-value represents the probability of any gene belonging to a biological disease.

AD.[57,74] We also established a new connection of the EGFR with AD-related targets such as APP, SNCA, LRP1, and NRG. Many bibliographic mentions also supported this finding. A recently published study has identified that APP-EGFR

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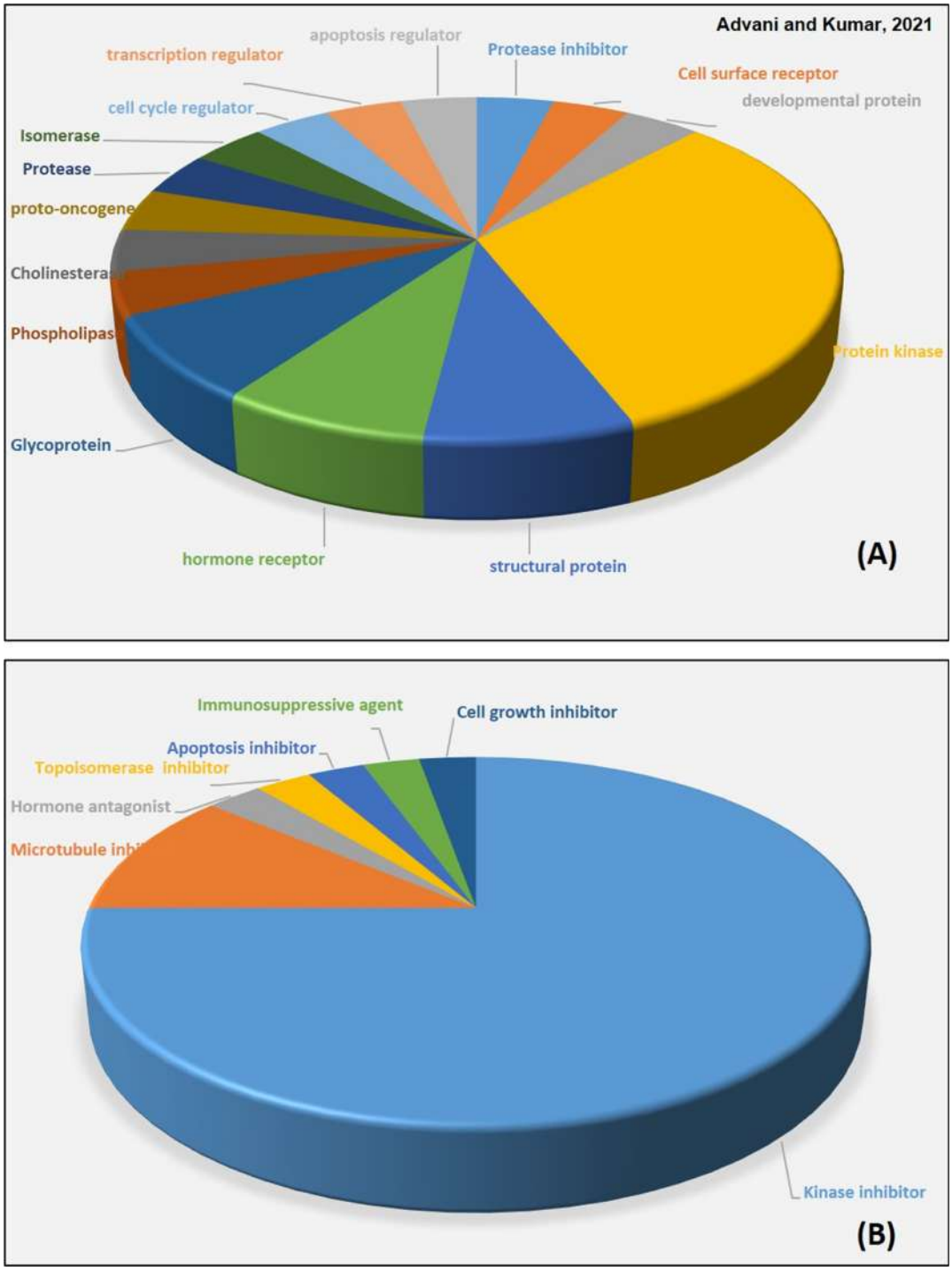

Figure 6. (A) Figure showing the functional categories of AD-related genes/PPI genes. The relative area of each segment corresponds to the relative fraction of a particular target class. As shown, protein kinases represent the major functional target protein class. (B) Functional classification of candidate repurposing anticancer drugs for AD. As expected, kinase inhibitors are the most prevalent drugs having neuroprotective functions.

interaction promoted extracellular signal-regulated kinase (ERK) signaling and contributed to neuritogenesis and neuronal differentiation.[75] Some studies have reported that the EGFR has structural and expression similarities with ErBb4, the primary receptor of NRG1, in several brain regions. Some studies have found that the EGFR was coexpressed with ErBb4 in several GABAergic neurons.[76,77] This finding would be helpful to establish new connections of EGFR inhibitors with NRG1. Although the role of the EGFR in SNCA gene polymorphisms in AD brains is not explored, a study by Yan *et al.* confirmed that SNCA plays a significant role in EGFR signaling in lung adenocarcinoma cells.[78]

Our proposed repurposed drug list had three EGFR inhibitors—vandetanib, erlotinib, and gefitinib. Among the proposed drugs, vandetanib, a tyrosine kinase inhibitor, is currently marketed to treat tumors of the thyroid gland. Likewise, erlotinib, an EGFR inhibitor, is used for treating nonsmall cell lung cancer (NSCLC) and pancreatic cancer.

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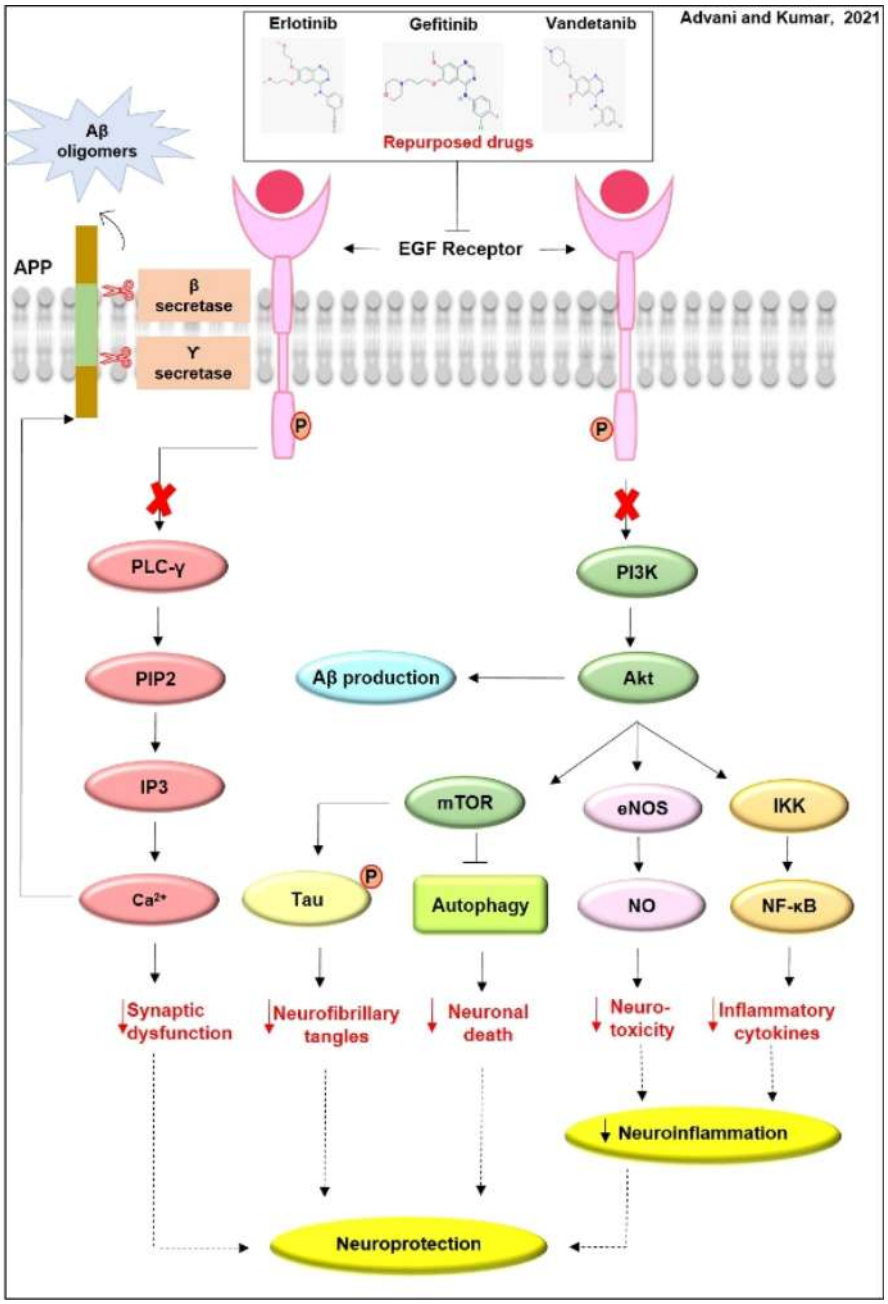

Figure 7. Schematic representation of the proposed mechanism of neuroprotective functions of EGFR inhibitors in AD. The binding of a ligand to the EGFR causes conformational changes in the receptor and activates various signaling cascades. Activation of the PI3K/Akt axis activates mTOR that is a major inhibitor of the autophagic process. The inhibition of autophagy leads to neuronal death. Activated mTOR is responsible for tau phosphorylation and Aβ production, the two major pathological hallmarks of AD. Activated Akt further induces endothelial nitric oxide synthase (eNOS) that generates nitric oxide (NO), a neurotoxin. The activated Akt instigates inflammatory cytokine production by inducing NF-κB production. The activated EGFR induces Ca^{2+} release from the endoplasmic reticulum by inducing phospholipase C gamma (PLC-γ) production. Excessive release of Ca^{2+} causes synaptic dysfunction and Aβ production from APP. All the events trigger neuroinflammation and neurodegeneration. Pharmacological inhibition of the EGFR by inhibitors, erlotinib, gefitinib, and vandetanib, may reverse the downstream signaling cascades of the EGFR and provide neuroprotection, a reduction in synaptic dysfunction, reduced tau phosphorylation, inhibition of neuronal death, and inhibition of neuroinflammatory processes. Dotted arrows represent the proposed neuroprotective functions of the repurposed drugs.

Similarly, gefitinib, an inhibitor of EGFR tyrosine kinase, is approved to treat locally advanced or metastatic NSCLC. Structural similarities of these drugs with approved AD drugs and physicochemical and BBB analyses also supported the therapeutic potential of these drugs. Earlier studies have proposed that erlotinib and gefitinib rescued EGFR-induced Aβ toxicity and memory loss in Drosophila and mouse models,[57] but the exact molecular mechanism and affected signaling pathways are yet to be elucidated.

Furthermore, some recent computational studies have predicted the potential drug−disease relations based on miRNA data. Based on this fact, we searched for miRNAs that were related to AD and correlated the gene targets of these miRNAs with the gene targets of the proposed

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repurposed drugs. From this analysis, we identified some neuroprotective microRNAs and established their relationship with the repurposed drugs. We identified miRNA-200a as a potential neuroprotective candidate that shares targets with all three repurposed EGFR inhibitors. In such a way, miRNA−disease−drug relations helped us to establish a link between repurposed drugs and AD concerning the miRNA axis.

To find out the significance of the results, we curated the available literature and proposed the potential neuroprotective functions of the repurposing drugs in AD pathogenesis, as shown in Figure 7. We suggested that tau phosphorylation, autophagy, and neuroinflammation were the significant AD-related biological mechanisms regulated by the proposed EGFR inhibitor drugs. PI3-Akt signaling, NF-kappa B pathway, and Ca^{2+} signaling were the significant pathways targeted by the proposed drugs.

5. CONCLUSIONS

Repurposed drugs can be a promising way of treating complex diseases such as AD. Our study has proposed an integrated omics-based data mining approach to identify the possible relationship of anticancer drugs with AD-associated genes. We further integrated network-based and pathway-based analysis methods to validate the overlap of anticancer drugs with AD-related pathways. The resulting drugs were validated based on computational repurposing tools, similarity scores, and physicochemical analysis. Additionally, literature validation, the functional similarity with miRNAs, and pathway analysis supported the hypothesis that EGFR inhibitors vandetanib, erlotinib, and gefitinib might play therapeutic roles by targeting AD-related proteins. Furthermore, we elucidated the mechanistic basis of these drugs in ameliorating AD-associated neurotoxicity and neuroinflammation. Additionally, our comprehensive approach also proposed a connection between AD-related targets and the reported repurposing drugs. As far as experimental aspects are concerned, *in vitro* and animal studies are warranted to confirm their neuroprotective potential.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c01526.

Functional enrichment analysis of AD-associated genes, list of candidate repurposing anticancer drugs, computational drug repositioning scores, physiochemical properties of repurposed drugs, and AD-related miRNAs, drugs, and targets (PDF)

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Author Contributions

P.K. conceived and designed the manuscript. D.A. collected and analyzed data. D.A. and P.K. wrote the manuscript, discussed the results, and analyzed the entire data.

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Notes

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■ ABBREVIATIONS

AD, Alzheimer's disease; ABL1, ABL proto-oncogene 1; Aβ, amyloid-β; ApoE, apolipoprotein E; APP, amyloid precursor protein; BBB, blood−brain barrier; BACE-1, beta-secretase; CDK4, cyclin-dependent kinase 4; CNS, central nervous system; CoDReS, computational drug repositioning score; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FDR, false discovery rate; FLT1, Fms-related receptor tyrosine kinase 1; GEO, Gene Expression Omnibus; GS2D, gene set to diseases; GWAS, genome-wide association studies; GSK3B, glycogen synthase kinase 3 beta; HMDB, Human Metabolome Database; HMDD, Human microRNA Disease Database; hTERT, human telomerase reverse transcriptase; IL-6, interleukin-6; KDR, kinase insert domain receptor; LRP1, LDL receptor-related protein 1; MAPK, mitogen-activated protein kinase; MCS, maximum common substructure; MIST, Molecular Interaction Search Tool; *M* log *P*, partition coefficient; NIH, National Cancer Institute; NRG1, neuregulin 1; NSCLC, nonsmall cell lung cancer; OR, odds ratio; PI3K-Akt, phosphatidylinositol-3-kinase; PPI, protein−protein interaction; PKA, protein kinase A; PS, presenilin; RAGE, receptors for advanced glycation end products; SNCA, alpha-synuclein; SNP, single-nucleotide polymorphism; STITCH, search tool for interactions of chemicals; TNF-α, tumor necrosis factor-alpha; TPSA, topological polar surface area; TTD, Therapeutic Target Database

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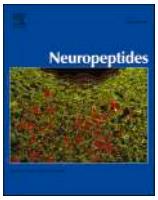

Deciphering the molecular mechanism and crosstalk between Parkinson's disease and breast cancer through multi-omics and drug repurposing approach

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ABSTRACT

Epidemiological studies indicate a higher occurrence of breast cancer (BRCA) in patients with Parkinson's disease. However, the exact molecular mechanism is still not precise. Herein, we tested the hypothesis that this inverse comorbidity result from shared genetic and molecular processes. We conducted an integrated omics analysis to identify the common gene signatures associated with PD and BRCA. Secondly, several dysregulated biological processes in both indications were analyzed by functional enrichment methods, and significant overlapping processes were identified. To establish common regulatory mechanisms, information about transcription factors and miRNAs associated with both the disorders was extracted. Finally, disease-specific gene expression signatures were compared through LINCS L1000 analysis to identify potential repurposing drugs for PD. The potential repurposed drug candidates were then correlated with PD-specific gene signatures by Cmap analysis. In conclusion, this study highlights the shared genes, biological pathways and regulatory signatures associated with PD and BRCA with an improved understanding of crosstalk involved. Additionally, the role of therapeutics was investigated in context with their comorbid associations. These findings could help to explain the complex molecular patterns of associations between PD and BRCA.

1. Introduction

Parkinson's disease (PD) is the second most prevailing neurodegenerative disorder characterized by progressive dopaminergic neuronal loss and intraneuronal alpha-synuclein aggregation. The complex neurodegenerative disorder is manifested by both motor and non-motor features that eventually appear during disease progression (Barker, 1991), (Kumar and Kumar, 2019). According to the latest reports by the Michael J. Fox Foundation for Parkinson's Research (MJFF), the annual medical and economic burden to the US government and its individuals due to PD is $51.9 billion annually. To date, several treatment regimens targeting the dopaminergic approach are available for PD treatment, but none of them effectively halt disease progression and are also associated with several issues such as motor complications, altered blood-brain barrier (BBB) permeability and less life span (Reddy et al., 2014), (Malavolta and Cabral, 2011).Therefore, it is difficult to achieve big breakthroughs through traditional treatments, and novel disease-modifying options are being explored (Mutt, 1992).

Recently, drug repurposing by computational methods has been emerged rapidly to discover new drug-disease relationships (Ashburn and Thor, 2004). Starting the drug development process with an existing drug bypasses the tedious and costly preclinical stages, and success rates have been reported to reach 30% (Reaume, 2011), (Marston and Wafford, 2017). The drugs repurposed for PD focused on enhancing the potency of the standard drug L-Dopa, however, its use is associated with motor complications. The earliest successful repurposing example in PD is Amantadine, an anti-viral agent that has been repurposed for treating PD-related motor symptoms(Hubsher et al., 2012).

Establishing disease-disease relationship allow the identification of shared mechanisms and open up a door for development of novel treatments. A considerable amount of evidences has established the overlapped clinical and molecular features of Alzheimer's disease (AD)

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and PD. Recently, an integrated approach based on transcriptomic signatures has identified the crosstalk between AD and PD by highlighting the common genes, pathways and miRNAs (Bisht et al., 2020). A number research groups are now involved to identify the potential overlap between PD and cancer. Epidemiological studies have reported an inverse association between PD and cancer, where many neoplasms are associated with lower cancer risk while some of them are found to be at higher risk (Ejma et al., 2020). However, both the indications are multifactorial, and their causal relationship is not clear yet, especially in the case of breast cancer (BRCA). Earlier studies have reported an

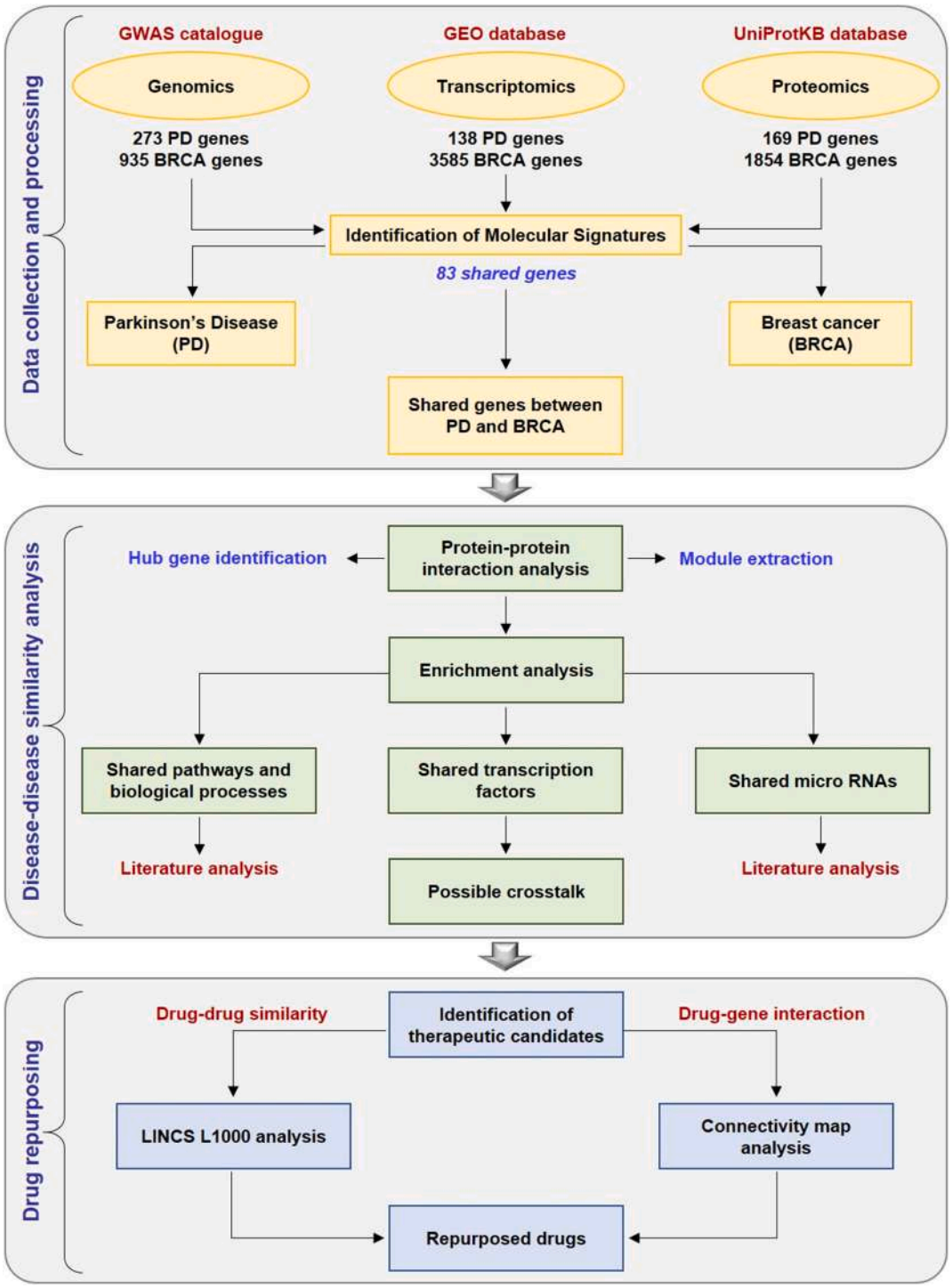


Fig. 1. Workflow overview: Data collection was performed from Genome-wide association studies catalog (GWAS) for genomic studies, Gene expression omnibus (GEO) database for transcriptomics studies and UniProtKB database for proteomics studies. After data processing, the intersection of Parkinson's disease (PD) and Breast cancer (BRCA) per omics layer was done using Venn diagrams. Protein-protein interaction (PPI) analysis extracted common hub genes to search for disease-disease similarity. These hub genes were further subjected to enrichment analysis and pathway analysis to obtain significant pathways and common GO terms. The common regulation of the two indications was further confirmed by identifying common transcription factors (TFs) and microRNAs (miRNA). LINCS L1000 and connectivity map (Cmap) analysis was performed to identify potential repurposing drugs for PD. The drug-drug and drug-gene similarity analysis has given potential repurposing drugs.

increased risk of breast cancer and higher mortality in women diagnosed with PD (Minami et al., 2000). A meta-analysis study has reported a lack of correlation between PD and risk of breast cancer. In a Danish population-based cohort study, an increased risk of grade 1 breast tumors was found in PD patients(Rugbjerg et al., 2012). A study published in the 2018 International Congress has claimed that females with breast cancer are at higher risk of developing PD when treated with chemotherapy drug tamoxifen (Mills-Joseph, 2018). Although the exact shared molecular mechanisms are unexplored, some studies have proposed that estrogen is neuroprotective and thus provides neuroprotection against PD (Van Den Eeden et al., 2003). Besides, mutations associated with many genes, including ATM (ataxia telangiectasia mutated), PARKIN and tumor suppressors the fact that increased levels of transcripts of the genes related to neurodegeneration, including Seladin-1, APP and PSEN1 are found in estrogen and progesterone receptor-negative (ER^-/PR^-) breast cancers (Nagai et al., 2004).

The present study is the first to explore the molecular association between PD and BRCA. We aimed to identify the common gene signatures associated with PD and BRCA by integrating multiple omics studies. We also used different enrichment methods and protein-protein interaction analysis methods to find commonly dysregulated pathways and the possible crosstalk between PD and BRCA. The next step was to identify the repurposed drugs for PD by establishing a drug-drug relationship with the approved BRCA drugs. Our findings have increased the understanding of common dysregulation between PD and BRCA, and this may further provide a way to explore new therapeutic agents. The complete pipeline is shown in Fig. 1.

2. Methodology

2.1. Data acquisition from GWAS, transcriptomic and proteomic studies

The genome-wide association studies (GWAS) data for PD and BRCA was downloaded from the NHGRI-EBI catalog that contains information about single nucleotide polymorphism (SNP)-trait associations (Buniello et al., 2019). For each SNP, information about associated allele, reported gene, *p*-value, associated trait, and study accession was collected. For the collection of transcriptome data, we browsed the GEO RNA-seq Experiments Interactive Navigator (GREIN) database, which is an interactive platform for analysis of GEO RNA seq data(Al Mahi et al., 2019). GSE 136666 contains information of RNA sequencing data of 8 PD and 8 control patients from substantia nigra and putamen regions. GSE52194 includes the mRNA expression profiles of 17 breast tumor samples of three different subtypes and normal breast tissue. The information about proteins associated with PD and BRCA was extracted from the UniProt Knowledgebase (UniProtKB), a platform to access functional information on proteins (Boutet et al., 2016). For each UniProtKB entry, the protein name and associated gene names were identified.

2.2. Data processing and analysis

Data processing and management were performed to process raw data into standardized tables for every omics layer. SNP functional annotation was performed by the rSNPBase database to identify SNP-related regulatory elements and their associated target genes(Guo et al., 2014). The raw transcriptomic data was processed to select genes with a false discovery ratio (FDR) ≤ 0.05 and the fold change (lof2FC) $= 2$. The proteomic data with missing gene names were removed, and that contained multiple gene names were separated. The next step was finding the intersection of the three omics layers to test is there any significant association between the three omics layers for PD and BRCA. The intersection was performed using the online tool InteractiVenn, which provides an online interface to construct Venn diagrams for different biological datasets(Heberle et al., 2015).

2.3. PPI network analysis

The PPI network was constructed by using an online tool NetworkAnalyst, by putting all the common genes as seed proteins. NetworkAnalyst provides a comprehensive platform for network analysis and visualization by integrating information available in different databases (Zhou et al., 2019). The topological parameters such as degree centrality and betweenness distribution were calculated by network analyzer in Cytoscape. Degree centrality correlates with the number of connections in the network and is a measure of influence that a node has on the network Likewise, the betweenness centrality of a node represents the number of shortest paths between the nodes that pass through the query node (Özgür et al., 2008). For reducing the hairball effect, we selected first order network for further analysis. In large and complex biological networks, Hairball effect critically affects the utility and significance of the nodes (Zhou et al., 2019). Additionally, the module explorer panel was used to identify the connected proteins referred to as modules in the network. The different modules were given ranks based on the number of seed proteins involved.

2.4. Identification of common regulatory signatures

To identify the common regulatory elements at transcriptional and post-transcriptional levels, the overlapping genes were searched against different databases to find common transcription factors (TFs) and microRNAs (miRNAs) for PD and BRCA. The TFs were identified against the JASPAR database, containing curated and non-redundant experimentally defined TF binding sites (Fornes et al., 2020). miRNAs were identified using the TarBase database, having experimentally validated miRNA targets of different species (Sethupathy et al., 2006). The TF-gene and miRNA-gene interaction networks were constructed and analyzed with NetworkAnalyst.

2.5. Pathway analysis

To understand the associated molecular functions, biological processes and signaling mechanisms, the identified overlapping genes were subjected to GO term analyses and pathway analyses with the online available tool Enrichr. Enrichr is an online search engine with >300 gene set libraries of 400,000 annotated gene sets(Xie et al., 2021). The <0.05 *P*-value cut-off was considered to select significant ontology terms. For pathway analysis, information related to three different databases-KEGG, Biocarta and Wiki pathways was retrieved.

2.6. Identification of repurposed drug candidates through LINCS L1000 and Cmap analysis

We identified the drugs indicated for PD and BRCA from multiple sources, including Drugbank and the National Cancer Institute (NCI) drug repository. The transcriptomic effects produced by PD-related drugs were generated using LINCS 1000 data by identifying consensus signatures for each drug. The iLINCS (Integrative LINCS) portal allows transcriptional analyses of different drug signatures based on the Board L1000 assay. To determine the drug similarities with existing BRCA drugs, a comparative analysis was performed with the signatures of existing BRCA drugs. The similarities were calculated based on the concordance scores. The BRCA drugs having a positive correlation with the available PD drugs were further analyzed by the connectivity map (Cmap) that integrates >1 million profiles of chemical, genetic and disease perturbations in different cell types (Lamb et al., 2006). The list of PD-related gene signatures was generated by functional enrichment analysis of the PD-associated genes found from three different omics layers. The connection of query drugs to PD-related gene signatures were analyzed using the Touchstone tool. The correlation was calculated based on the CMap connectivity scores ranging from −100 to 100. Drugs showing a negative correlation with PD gene signatures were considered

the potential repurposing candidates in reversing PD-related symptoms.

2.7. Scoring and ranking of repurposed drugs

The drugs obtained from the previous step were used as an input to CoDReS (Computational Drug Repositioning Score) tools. The tool assigns a functional score (FS) and a structural score (StS) to each drug with respect to the disease of interest and gives a combined repurposing score (CoDReS) or a priori score (aS) (Karatzas et al., 2019).

3. Results

3.1. Omics analysis links PD signatures with BRCA signatures

From 54 GWAS studies for PD, we identified 390 SNPs, while for 101 GWAS studies for BRCA, we found 1455 SNPs, out of which 211 SNPs were found functionally annotated with PD and 742 SNPs with BRCA. The PD-related SNPs were functionally annotated with 273 target genes, while BRCA related SNPs were associated with 935 different genes. For transcriptomic data, out of the 138 significant PD-associated genes, 50 genes were upregulated, and 88 genes were downregulated, while out of 3585 significant BRCA associated genes, 2695 were upregulated, and 890 genes were downregulated. The greatest fold differential expression for PD was observed 2.08-fold upregulation of RPS3AP3 gene and 2.05-fold downregulation of TPH2 gene. In the case of BRCA, the greatest 16.84-fold upregulation was for the RNVU1–7 gene and downregulation of 10.722- fold for the IL-6 gene. Similarly, we found 188 and 2628 proteins for PD and BRCA from the UniProtKB database that was related to 169 and 1854 genes, respectively. The combined data of the three omic layers per disease is provided in Supplementary Table 1.

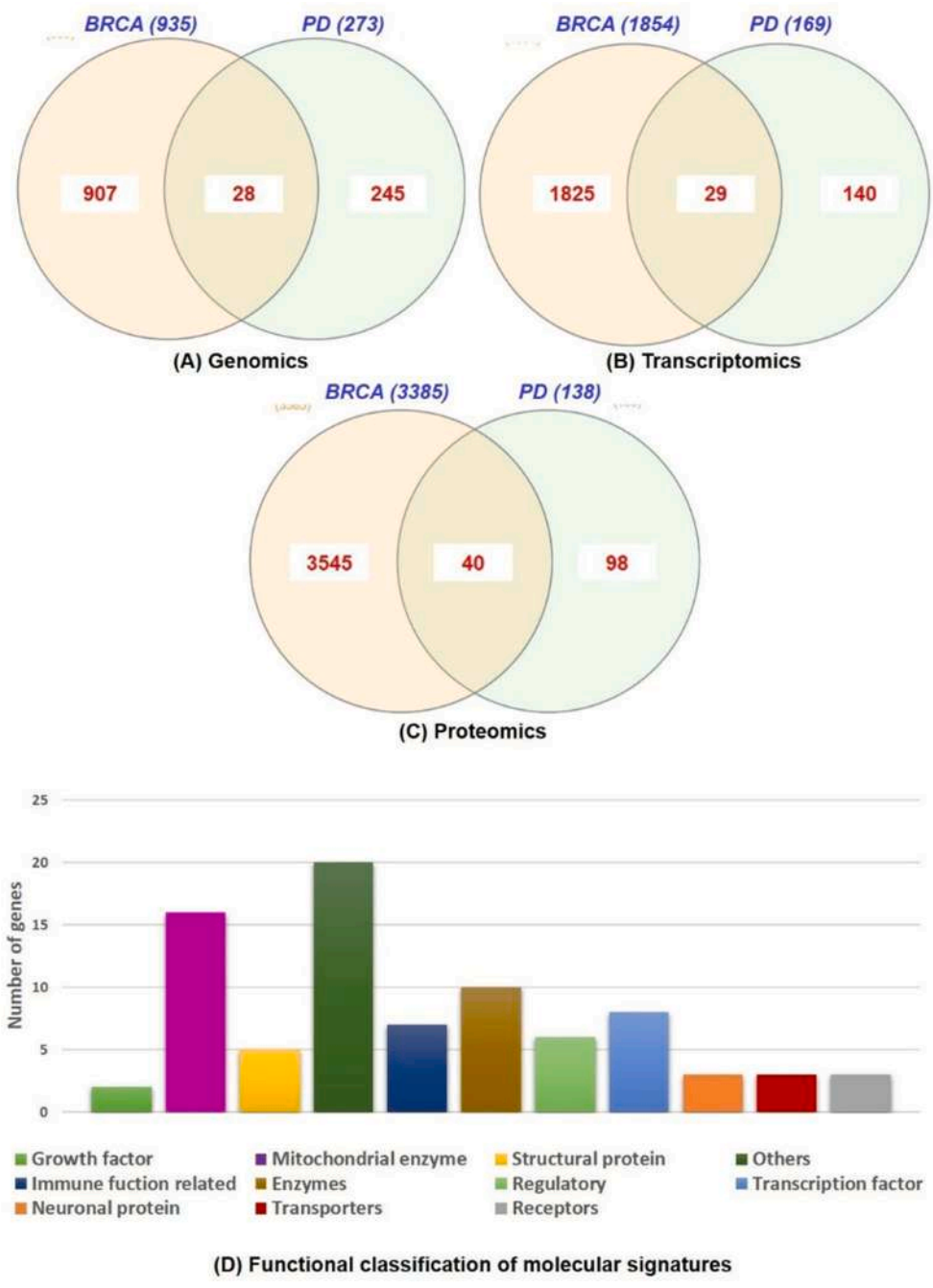


Fig. 2. (A-C) Venn diagrams showing the overlap between genes obtained from genomic studies (A), transcriptomics studies (B), and proteomics studies (C) for breast cancer (BRCA) and Parkinson's Disease (PD). Significant overlaps have shown a significant number of shared genes for different omics layers. (D) The proteins encoded by the significant genes belong to different functional categories. We found mitochondrial enzymes, other enzymes and transcription factors as the top three significant functional categories. The number of genes are showing on the Y-axis.

To establish the common linkage between PD and BRCA at the molecular level, we identified different intersections between the two diseases per omics layer. For genomics, we identified 28 shared genes, for transcriptomics 40 genes and for proteomics 29 genes, as shown in the Venn diagrams (Fig. 2A-C). To identify the total number of shared genes between PD and BRCA, we combined the shared genes per omics layer resulted in 96 shared genes, out of which 13 belonged to non-coding proteins and were thus excluded from the study. The expressed proteins of the 83 shared genes were analyzed for the functional categories (Fig. 2D). We found different categories- others (24%), mitochondrial enzymes (19%), other enzymes (12%), transcription factor (10%), immune function-related proteins (8%), structural protein (6%), regulatory proteins (7%), neuronal protein (4%), transporters (4%), receptors (4%), and growth factor (2%). We found most of the proteins were related to mitochondrial processes and electron transport chain.

3.2. PPI network analysis identifies dysregulated genes linking PD and BRCA

The shared interactants of Venn analysis of different omics data were combined to identify common gene signatures between PD and BRCA. We reported 83common genes, which were then mapped in the form of protein-protein interaction (PPI) network. The PPI network was constructed to predict the significant biological interactions that play a key role in linking PD and BRCA. The resultant PPI network had 10 different subnetworks comprising a different number of nodes and interconnecting edges. We selected the largest subnetwork with 434 nodes and 472 edges for further analysis. To minimize the 'hairball effect', we constructed PPI network of first-order having seed nodes and other connecting nodes (Fig. 3A). The PPI network was further assessed for different topological parameters, including degree centrality and betweenness. We observed degree with a range of 1 to 54 and betweenness with a range of 0 to 51,830.58. We found that out of 434

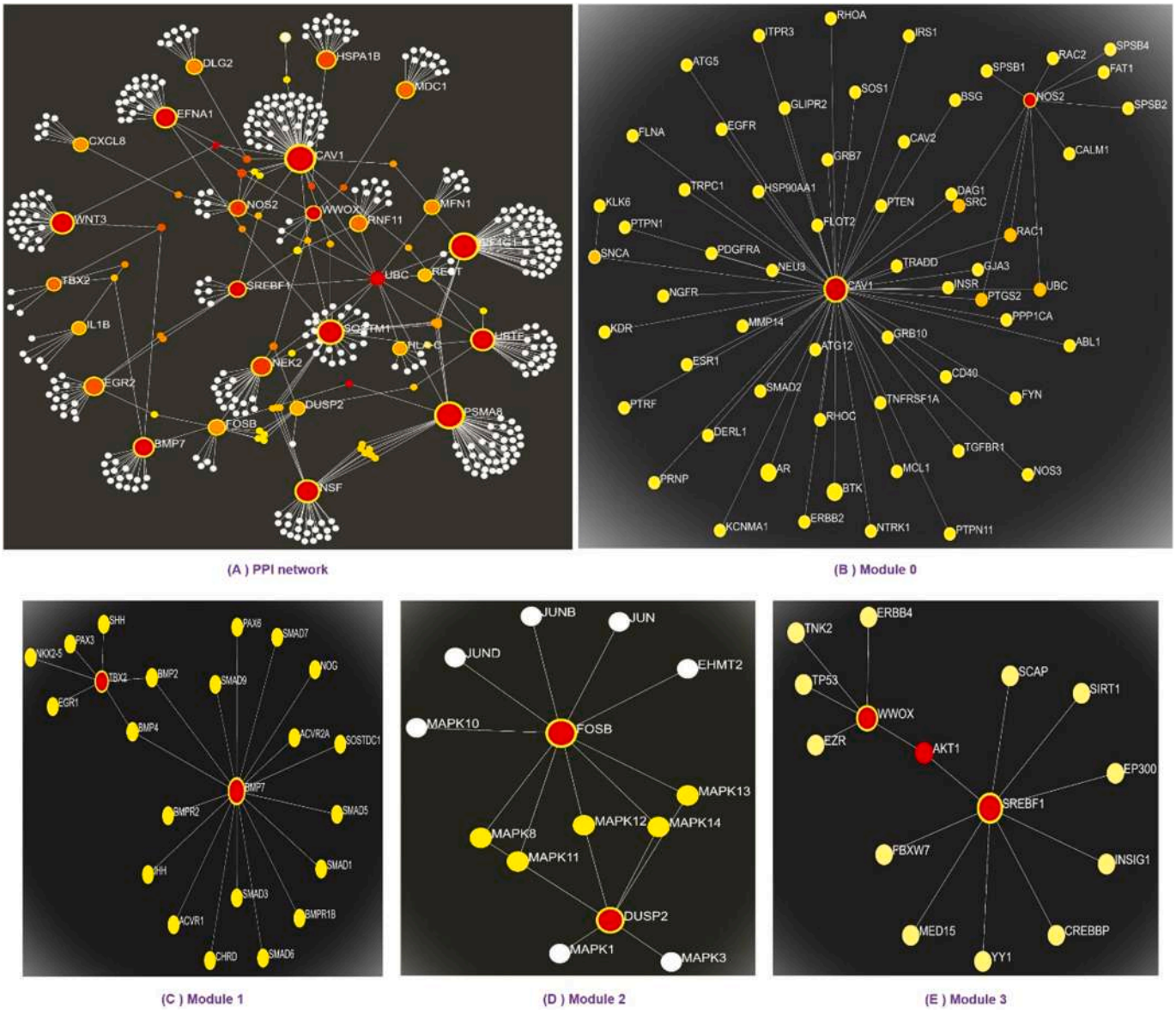


Fig. 3. (A) Protein-protein interaction (PPI) network showing the hub genes where nodes represent the proteins and edges represent the connection. The query protein nodes are highlighted in yellow. The size of different nodes corresponds to their degree centrality values in the network. Different significant modules have been extracted from the PPI network, and the top four modules were selected for further analysis. (B) Module 0 has three query nodes CAV1, NOS2 and KLK6. (C-E) Module 1 to module 3 have two query nodes each- module 1 has BMP7 and TBX2, module 2 has DUSP2 and FOSB and module 3 has WWOX and SREBF1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

nodes, 18 nodes had degree centrality value of ≥10. The nodes with higher values of degree were considered as hub nodes, while those with higher betweenness value were considered as bottleneck nodes. We found CAV1 (degree-54; betweenness-38,225.17), PSMA8 (degree-47; betweenness-27,751.2), EIF4G1 (degree-47; betweenness-17,641.86), SQSTM1 (degree-36; betweenness-17,059.53), and NSF (degree-29; betweenness-8703.19) as the top 5 hub nodes with highest values of degree in the network. These hub genes can be considered as the possible therapeutic targets as they are involved with shared signaling pathways. The description of all the hub proteins with topological parameters is provided in Table 1.

The PPI network was further evaluated for module analysis to extract different modules having similar biological functions. We observed 22 different modules with p-value ≥0.05 and ranged in size from 5 to 61 genes. We selected the top 4 modules having different hub nodes interacting with different genes (Fig. 3B-E). Module 0 (*p*-value 5.94E-17) consisted of CAV1, NOS2 and KLK6 as hub nodes, module 1 (p-value 8.76E-09) had TBX2 and BMP7 hub nodes, module 2 (p-value 2.24E-05) had DUSP2 and FOSB hub nodes, and module 4 (p-value 0.00424) had SREBF1 and WWOX hub nodes.

3.3. Identification of regulatory molecules establishes a common link between PD and BRCA

To decode the disease-disease association at transcriptional and post-transcriptional levels, we found the connection of the hub genes with TFs and miRNAs, as shown in Fig. 4A-B. GATA2, NFIC, NFKB1, USF2, FOS, HOXA5, TP53, CEBPB, ELK1, and SRF were selected as the top interacting TFs with the hub genes. All the TFs play different roles in the pathogenesis of PD and BRCA (Table 2).

Similarly, hsa-mir-93-5p, hsa-mir-1-3p, hsa-mir-106a-5p, hsa-mir-17-5p, hsa-mir-218-5p, hsa-mir-106b-5p, hsa-mir-149-3p, hsa-mir-16-5p, hsa-mir-192-5p, hsa-mir-34a-mir, hsa-mir-215-5p, hsa-mir-484, hsa-mir-744-5p were identified as the top interacting miRNAs with the hub genes. The relevance of these miRNAs in both PD and BRCA was identified and shown in (Table 2).

Table 1
Description of hub proteins with topological parameters.

Protein	Description	Degree	Betweenness
CAV1	Caveolin-1	54	38225.17
PSMA8	Proteasome 20S subunit alpha 8	47	27751.2
EIF4G1	Eukaryotic translation initiation factor 4 gamma 1	47	17641.86
SQSTM1	Sequestosome-1	36	17059.53
NSF	N-Ethylmaleimide sensitive factor, vesicle fusing ATPase	29	8703.19
WNT3	Wnt family member 3	26	13016.88
UBTF	Upstream binding factor 3	26	10516.1
EFNA1	Ephrin A1	22	8355.92
BMP7	Bone morphogenetic protein 7	18	9829.46
NEK2	NIMA Related Kinase 2	18	6896.85
EGR2	Early growth response 2	16	5822.35
HSPA1B	Heat Shock Protein Family A (Hsp70) Member 1B	15	5957
UBC	Ubiquitin C	13	51830.58
MDC1	Mediator of DNA damage checkpoint 1	12	4697
SREBF1	Sterol Regulatory Element Binding Transcription Factor 1	11	9330.41
NOS2	Nitric oxidase synthase 2	11	6741.53
RNF11	Ring finger protein 11	11	3952.14
FOSB	Fos proto-oncogene, AP-1 transcription factor subunit	10	2623.37

Highlighted rows represent the top 5 hub proteins.

3.4. Pathway analysis identifies overlapping over-represented pathways and gene ontologies associated with PD and BRCA

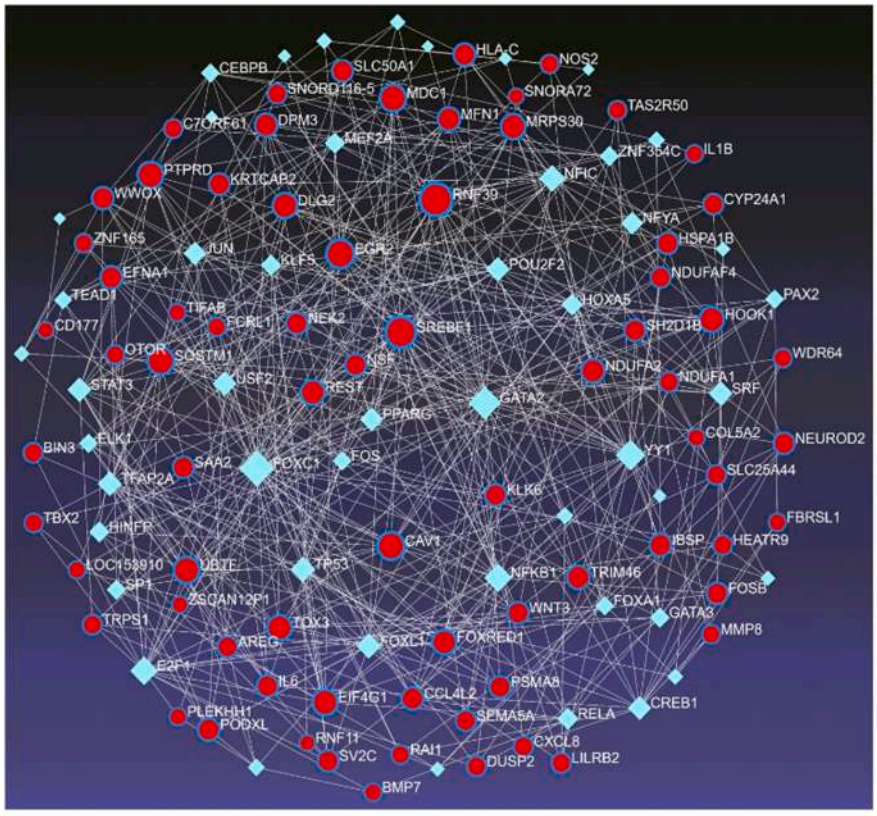
To sketch the common pathway dysregulation between PD and BRCA, we performed pathway enrichment and gene ontology analysis of the hub genes. We reported 10 enriched KEGG pathways Prion disease (*P*-value 2.14E-18), oxidative phosphorylation (P-value 8.12E-17), pathways of neurodegeneration (P-value 5.97E-16), Alzheimer's disease (P-value 7.54–16), Parkinson's disease (P-value 3.11E-15), thermogenesis (P-value 1.86E-14), Diabetic cardiomyopathy (P-value 4.72E-14), Huntington disease (P-value 9.28E-14), and Amyotrophic lateral sclerosis (P-value 1.19E-13) having >10 overlapping genes in both disorders. From Bioplanet database, oxidative phosphorylation (P-value 1.14E-16), Parkinson's disease (P-value 6.43E-17), and electron transport chain (P-value 2.07E-18) were found enriched. From Wiki pathways, we found the electron transport chain (P-value 1.53E-18), mitochondrial complex I assembly (P-value 1.19E-13), and non-alcoholic fatty liver disease (P-value 3.72E-09) as enriched pathways. These results revealed that pathways enriched with the maximum number of shared genes were associated with electron transport chain and oxidative phosphorylation.

The comparative analysis of different enriched pathways from different databases is shown in Fig. 5A-C. Similarly, we identified the significant GO terms (biological processes, cellular function and molecular function) shared between PD and BRCA. We found regulation of interleukin-6 production (GO:0032755;5 genes), mitochondrial respiratory chain complex I assembly (GO:0032981; 4 genes), NADH dehydrogenase complex assembly (GO:0010257;4 genes), positive regulation of interleukin-8 production (GO:0032757;4 genes) and regulation of neurogenesis (GO:0050767;4 genes) as the top 5 biological processes comprised of the maximum number of common genes. The complete list of top ontology terms identified is shown in Table 3.

3.5. LINCS L1000 and Cmap analysis identifies potential repurposing drug candidates based on gene expression signatures

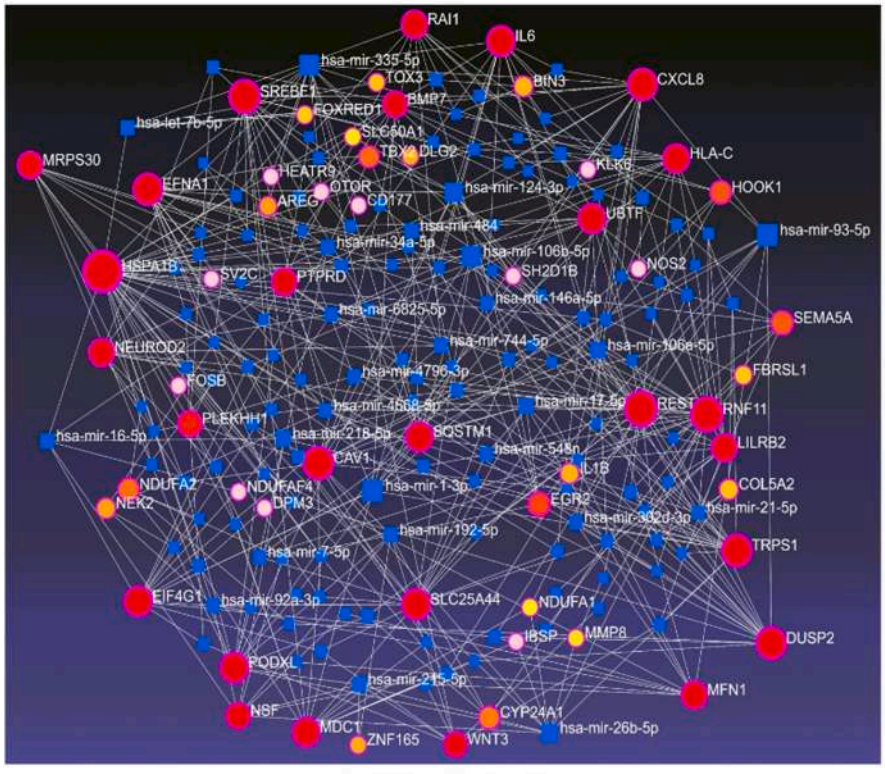
To investigate the potential role of BRCA drugs in PD treatment, we explored the gene expression signatures generated by the drugs for the two indications. First, we obtained the drug list for PD from Drugs.com. The information on BRCA drugs was retrieved from the National Cancer Institute's (NCI) comprehensive database that contains information of the FDA-approved and investigational cancer drugs and combinations. We collected 38 approved breast cancer drugs by omitting information of any investigational drugs and drug combinations. Further, the consensus signatures for each PD drug were obtained from the LINCS L1000 database and compared with consensus signatures of BRCA drugs. The BRCA drugs with a positive correlation with PD drugs were considered for further analysis. We found positive correlations of BRCA drugs with seven PD drugs. The observed correlations were plotted in the form of a heat map where the red color represents positive correlation and the blue color represents no correlation (Fig. 6A). For instance, tolcapone, a catechol-*O*-methyl transferase (COMT) inhibitor was correlated with a maximum of eleven BRCA drugs- alpelisib, anastrozole, doxorubicin, Fluorouracil, lapatinib, mitoxantrone, olaparib, palbociclib, raloxifene, thiotepa and toremifene. Similarly, rasagiline, an irreversible monoamine oxidase B (MAOB) inhibitor was related with six BRCA drugs-alpelisib, everolimus, lapatinib, mitoxantrone, neratinib, and palbociclib. The dopamine precursor levodopa used for PD treatment was correlated with five BRCA drugs- lapatinib, mitoxantrone, olaparib, palbociclib, and tamoxifen. Selegiline, another MAOB inhibitor was related to four BRCA drugs- cyclophosphamide, lapatinib, mitoxantrone, and neratinib. For carbidopa, a dopa decarboxylase inhibitor, we found two BRCA drugs- lapatinib and neratinib; for pramipexole, a dopamine agonist, only one drug- raloxifene and for benztropine, an anticholinergic, only one drug- cyclophosphamide.

To further support our drug repurposing strategy, we explored the



(A) TF-gene interaction network

TF	Degree
FOXC1	43
GATA2	33
YY1	27
E2F1	22
NFKB1	22
NFIC	19
FOXL1	16
TP53	16
POU2F2	15
SRF	15



miRNA	Degree
hsa-mir-335-5p	15
hsa-mir-124-3p	12
hsa-mir-26b-5p	10
hsa-mir-1-3p	9
hsa-mir-93-5p	9
hsa-mir-106a-5p	8
hsa-mir-218-5p	7
hsa-mir-106b-5p	7
hsa-mir-17-5p	7
hsa-mir-484	6

(B) miRNA-gene interaction network

Fig. 4. (A) Transcription factor-hub gene network shows the interaction between the hub genes and associated transcription factors (TFs). The red circles represent the hub genes and the blue diamonds represent the associated TFs. (B) miRNA-gene interaction network links the hub genes through miRNAs. The red circles represent the hub genes and the blue squares represent the miRNAs. The associated tables show the top interacting TFs and miRNAs with their degree centrality values. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Summary of top transcription factors and miRNAs associated with hub genes with their significance in PD and BRCA pathogenesis.

Common transcription factors			
Factor	Associated hub genes	Significance in PD	Significance in BRCA
GATA2	ZSCAN12P1, NDUFAF4, MFN1, BIN3, SQSTM1, PTPRD, BIN3, CCL4L2, WWOX, UBTF, SAA2, EIF4AG1	Transcriptional regulation of SNCA gene expression	Associated with breast cancer progression by epigenetic regulation of G9a (Casciello et al., 2017)
NFIC	HSPA1B, NEK2, UBTF, NDUFA2, CYP24A1, MRPS30, FOXRED1, DLG2	Serves as a regulatory transcriptional signature in PD (Faruqui et al., 2021)	Regulation of breast cancer progression via NFI-C-KLF4-E-cadherin pathway (Lee et al., 2015)
NFKB1	IL6, PODXL, SAA2, SQSTM1, NDUFA2, CCL4L2, EIG4G1, FOXRED1	Production of inflammatory mediators responsible for neurotoxicity (Flood et al., 2011)	Promotes tumor development, progression and chemoresistance in hormone-independent forms of breast cancer (Wang et al., 2015)
USF2	CCL4L2, WWOX, EIF4G1, PTPRD, SQSTM1, PODXL, MFN1	NA	Highly expressed in breast cancer and assists tumor progression (Tan et al., 2019)
FOS	IL6, IBSP, SQSTM1, PTPRD, SAA2, WWOX	Regulation of L-Dopa–induced dyskinesia (LID) (Beck et al., 2019)	Regulation of tumor invasion and metastasis (Milde-Langosch et al., 2004)
HOXA5	BIN3, NDUFA2, FOXRED1, DLG2, NEK2, IBSP	NA	Overexpression is associated with the p53-dependent apoptotic pathway (Chen et al., 2004)
TP53	NDUFA2, FOXRED1, PTPRD, EIF4G1, UBTF	Functions as an anti-autophagic TF. Transcriptional repression of PINK1 (Checler et al., 2018)	Frequently mutated in BRCA, especially in triple-negative breast cancer (Duffy et al., 2018)
CEBPB	WWOX, PTPRD, SQSTM1, MRPS30	Regulation of cleavage of α-synuclein and monoamine oxidase B activity (Wu et al., 2020)	Regulation of breast cancer cell invasion and migration through PAK4-CEBPB-CLDN4 axis (Wang et al., 2019)
ELK1	NEK2, BIN3, MFN1, UBTF	Cytoplasmic phosphorylation of the protein is associated with protein inclusions in PD (Besnard et al., 2011)	Promotes breast cancer cell proliferation (Ahmad et al., 2017)
SRF	DLG2, NDUFA2, CYP24A1, SQSTM1	Important regulator of anti-apoptotic response in dopaminergic neurons (Rieker et al., 2012)	Induction of mammary stem cell-like properties in BRCA (Kim et al., 2015)
Common miRNAs			
hsa-mir-335-5p	IL6, EFNA1, HSPAIB, CXCL8, REST, SQSTM1, NEUROD2, WNT3, HOOK1, SREBF1, AREG	Regulation of inflammation by targeting LRRK2 (Oliveira et al., 2021)	Regulation of BRCA1 gene expression (Heyn et al., 2011)
hsa-mir-124-3p	CXCL8, TBX2, PODXL, EGR2, EFNA1, TRPS1, IL6, REST, DUSP2, CAV1, HSPAIB	Associated with neuroprotective properties by regulation of the ERK pathway (Dong et al., 2018)	Contributes to breast cancer tumorigenesis and targets Cbl prot-oncogene (Wang et al., 2016)
		NA	

Table 2 (*continued*)

Common transcription factors			
Factor	Associated hub genes	Significance in PD	Significance in BRCA
hsa-mir-26b-5p	MMP8, CYP24A1, NSF, PODXL, CAV1, TRPS1, RNF11, NDUFA1, SLC25A44		Functions as a radiation biomarker in BRCA (Wilke et al., 2018)
hsa-mir-1-3p	UBTF, BMP7, IL6, CXCL8, EIF4G1, TRPS1, MDC1, PTPRD, HOOK1	NA	Mediates breast cancer invasion and metastasis (Tao et al., 2021)
hsa-mir-93-5p	SLC25A44, DUSP2, REST, HOOK1, CXCL8, EGR2, MFN1, CAV1, SQSTM1	NA	Controls epithelial-mesenchymal-transition in breast cancer cells (Xiang et al., 2017)
hsa-mir-106a-5p	DUSP2, REST, ILIB, IL6, CXCL8, MFN1, CAV1, SLC25A44	Associated with cognitive improvement in PD brains (Da Silva et al., 2021)	Serves an important biomarker for breast cancer progression(Chen et al., 2019)
hsa-mir-218-5p	TRPS1, SEMA5A, EFNA1, EIF4G1, PODXL, NSF, CYP24A1	Has neuroprotective effects on dopaminergic neurons (Ma et al., 2021)	Activation of Wnt signaling and regulation of breast cancer metastasis (Taipaleenmäki et al., 2016)
hsa-mir-106b-5p	DUSP2, HSPA1B, REST, SQSTM1, MFN1, CAV1, SLC25A44	NA	Regulation of breast cancer progression by suppression of PI3K/Akt pathway (Li et al., 2017)
hsa-mir-17-5p	SCL25A44, SQSTM1, DUSP2, REST, EGR2, MFN1, CAV1	Associated with PD (Su et al., 2018)	Acts as both tumor promoter and tumor suppressor (Bozgeyik, 2020)
hsa-mir-484	RNF11, HSPA1B, UBTF, HLA—C, SQSTM1, SREBF1	NA	Changes cytidine deaminase activity associated with breast cancer proliferation and chemoresistance (Ye et al., 2015)

NA represents TFs and miRNAs for which no literature study is available.

connections of BRCA drugs with PD gene signatures (Supplementary Table 2). We observed that only a few BRCA drugs were correlated with PD gene signatures. We considered negative correlations that mean the drug can reverse the effects of the associated gene signatures and is thus considered a potential repurposing drug. We found 11 BRCA drugs with good connectivity scores with PD gene signatures. The observed drug-gene correlations were shown in a heat map where the red color represents positive correlations, and the blue color represents negative correlations (Fig. 6B).

3.6. CoDReS re-ranking prioritized potential repurposing drugs for Parkinson's disease

The repurposed drugs from CMap and LINCS L1000 analysis were analyzed for the structural and functional properties. The comparative structural, functional and composite scores were represented in Fig. 7. The values have indicated that most of the drugs have similar structural scores but functional scores have great variations. We found that four drugs- palbociclib, cyclophosphamide, olaparib and thiotepa have structural score value 1 and only one drug tamoxifen has functional score value 1. It was observed that anastrazole was assigned with 0 value in terms of both structural and functional scores. The drugs were ranked based on their composite CoDReS scores and tamoxifen, raloxifene, palbociclib, cyclophosphamide, and olaparib were the top 5 drugs. We considered the selective estrogen receptor modulators- tamoxifen and raloxifen with the highest CoDReS scores as the most promising

Fig. 5. Graphical representation of the enriched pathways of shared genes between PD and BRCA. (A) KEGG pathways, (B) Bioplanet pathways and (C) Wiki pathways. Each color represents a different pathway and the numbers represent the total number of genes associated with a specific pathway. For KEGG pathways, pathways of neurodegeneration (22 genes), Alzheimer's Disease (20 genes), and Prion disease (20 genes) are the most enriched pathways. For Bioplant pathways, oxidative phosphorylation, Parkinson's disease and electron transport chain, each with 15 genes, are the top three significant pathways. Similarly, for Wiki pathways, electron transport chain (15 genes), non-alcoholic fatty liver disease (10 genes), and mitochondrial complex I assembly (10 genes) are the significant pathways.

Table 3
Top 10 ontology terms associated with hub genes in PD and BRCA.

Term	P-value	Genes involved
Biological process		
Regulation of cell adhesion molecule production (GO:0060353)	8.82E-06	CXCL8;CAV1;IL1B
Positive regulation of neuroinflammatory response (GO:0150078)	2.28E-05	IL6;IL1B;MMP8
Positive regulation of interleukin-6 production (GO:0032755)	3.24E-05	IL6;NOS2;IL1B;LILRB2;MMP8
Negative regulation of nervous system development (GO:0051961)	9.82E-05	IL6;REST;IL1B
Regulation of neuroinflammatory response (GO:0150077)	9.82E-05	IL6;IL1B;MMP8
Mitochondrial respiratory chain complex I assembly (GO:0032981)	1.73E-04	NDUFAF4;NDUFA2;NDUFA1; FOXRED1
NADH dehydrogenase complex assembly (GO:0010257)	1.73E-04	NDUFAF4;NDUFA2;NDUFA1; FOXRED1
Regulation of interleukin-6 production (GO:0032675)	1.89E-04	IL6;NOS2;IL1B;LILRB2;MMP8
Positive regulation of interleukin-8 production (GO:0032757)	2.11E-04	IL6;NOS2;IL1B;HSPA1B
Regulation of neurogenesis (GO:0050767)	2.25E-04	IL6;REST;IL1B;WNT3
Cellular function		
Mitochondrial respiratory chain complex I (GO:0005747)	0.001074	NDUFA2;NDUFA1;FOXRED1
Respiratory chain complex I (GO:0045271)	0.001074	NDUFA2;NDUFA1;FOXRED1 CYP24A1;NDUFAF4;
Mitochondrial inner membrane (GO:0005743)	0.00501	NDUFA2;NDUFA1;MRPS30; FOXRED1 CYP24A1;NDUFAF4;
Organelle inner membrane (GO:0019866)	0.006462	NDUFA2;NDUFA1;MRPS30; FOXRED1
Endocytic vesicle membrane (GO:0030666)	0.007097	CAV1;HLA-C;AREG;WNT3 CYP24A1;NDUFAF4;
Mitochondrial membrane (GO:0031966)	0.007412	NDUFA2;MFN1;NDUFA1; MRPS30;FOXRED1
Aggresome (GO:0016235)	0.012239	SQSTM1;HSPA1B
Anchored component of plasma membrane (GO:0046658)	0.020577	EFNA1;CD177
Mitochondrial envelope (GO:0005740)	0.023292	NDUFAF4;NDUFA2;NDUFA1
Filtration diaphragm (GO:0036056)	0.023773	PODXL
Molecular function		
Cytokine activity (GO:0005125)	1.87E-04	IL6;CXCL8;CCL3L1;IL1B; BMP7;WNT3
Ionotropic glutamate receptor binding (GO:0035255)	0.001001	NSF;SQSTM1
Glutamate receptor binding (GO:0035254)	0.002959	NSF;SQSTM1
Receptor ligand activity (GO:0048018)	0.003637	SEMA5A;IL6;IL1B;AREG; BMP7;WNT3
NADH dehydrogenase (quinone) activity (GO:0050136)	0.012239	NDUFA2;NDUFA1
NADH dehydrogenase (ubiquinone) activity (GO:0008137)	0.012239	NDUFA2;NDUFA1
Growth factor receptor binding (GO:0070851)	0.014119	IL6;IL1B;AREG
Chemokine activity (GO:0008009)	0.020577	CXCL8;CCL3L1
Syndecan binding (GO:0045545)	0.023773	SEMA5A
Chemokine receptor binding (GO:0042379)	0.024056	CXCL8;CCL3L1

repurposed drugs for PD. The comparative scores of different drugs are given in Supplementary Table 3 (S3).

4. Discussion

Human diseases are associated with a complex and dynamic molecular network. Multi-omics integration provides a complete picture of the contributing factors to reveal crosstalk patterns of the involved disease conditions. Drug repurposing based on common disease mechanisms is a new approach to discover new therapeutic avenues. Numerous studies have established a connection between cancer and neurodegeneration. A recent study has found a transcriptomic and genetic association between AD, PD and cancer (Forés-martos et al., 2021). Additionally, a meta-analysis study has revealed evidence of inverse comorbidity between different central nervous system disorders (AD, PD, and schizophrenia) and cancers (lung, prostate, and colorectal). However, no study has signified the correlation between PD and BRCA. We found positive patterns of associations between PD and BRCA, and it agrees with the previous reports highlighting a common risk factor between PD and BRCA. To the best of our knowledge, the present study is the first to dissect the common molecular mechanism between PD and BRCA at the multi-omics level and to identify the repurposed drugs for PD from the available pool of BRCA drugs BRCA. We combined the data from three different omics layers (genomics, transcriptomics and proteomics) and analyzed the associated pathways, biological processes and therapeutic molecules. From the integrated analysis, we identified the total number of overlapping genes between PD and BRCA. We found 28 overlapping genes from genomics, 40 genes from transcriptomics and 29 genes from proteomics studies. We found that the total number of overlapping genes on genomics and proteomics layers were relatively low than the transcriptomics layer.

We identified different hub genes based on topological parameters. These hub genes are assumed to play a crucial role in disease pathogenesis and are associated with several biological processes in PD and BRCA, as reported in the literature. The protein with the highest degree in the network is Caveolin-1 (CAV1), the major component of the caveolae plasma membranes. A recent study has reported that CAV-1 expression is associated with increased neuronal α-syn uptake and inclusion body formation in PD brains (Ha et al., 2021). Similarly, Cav1 plays a crucial role in breast cancer progression, invasion, migration, metastasis, autophagy and invasion (Qian et al., 2019). Another essential protein, Proteasome 20S Subunit Alpha 8 (PSMA8), is a component of spermatoproteasome. Although the role of PSMA8 in PS and BRCA is not well established, a recent study has demonstrated an indirect link between PSMA8 and PARK2 proteins (Botelho et al., 2020). The protein encoded by EIF4G1 is the component of the eIF4F complex required for eukaryotic protein translation initiation. A study has established that missense mutation in EIF4G1 is associated with mRNA translation initiation in familial PD (Chartier-Harlin et al., 2011). Overexpression of EIF4G1 is associated with inflammatory breast cancer tumor development (Silvera et al., 2009). Sequestosome-1 (SQSTM1) is another hub protein regulating the nuclear factor kappa-B (NF-kB) signaling pathway. In PD, SQSTM1/p62 interacts with LRRK2, promotes its autophagic clearance, and also promotes the formation of paired helical filament (PHF)-tau and α-synuclein inclusions by interacting with ubiquitin (Ma et al., 2019). Similarly, in BRCA, the protein has been found to induce cell cycle arrest and tumor microenvironment modulation and thus regulates breast cancer cell progression (Qi et al., 2021). N-Ethylmaleimide Sensitive Factor, Vesicle Fusing ATPase (NSF) is the protein required for vesicle-mediated transport. It has been shown that aberrant phosphorylation of NSF by LRRK2 is responsible for altered synaptic vesicle dynamics in PD (Belluzzi et al., 2016). The WNT3 gene is a member of the WNT gene family and is involved in the WNT signaling pathway. The exact mechanism of WNT3 in PD is unknown, however, a GWAS study has reported the role of WNT3 in PD pathogenesis (Liu et al., 2011). A study has highlighted the role of WNT3 in

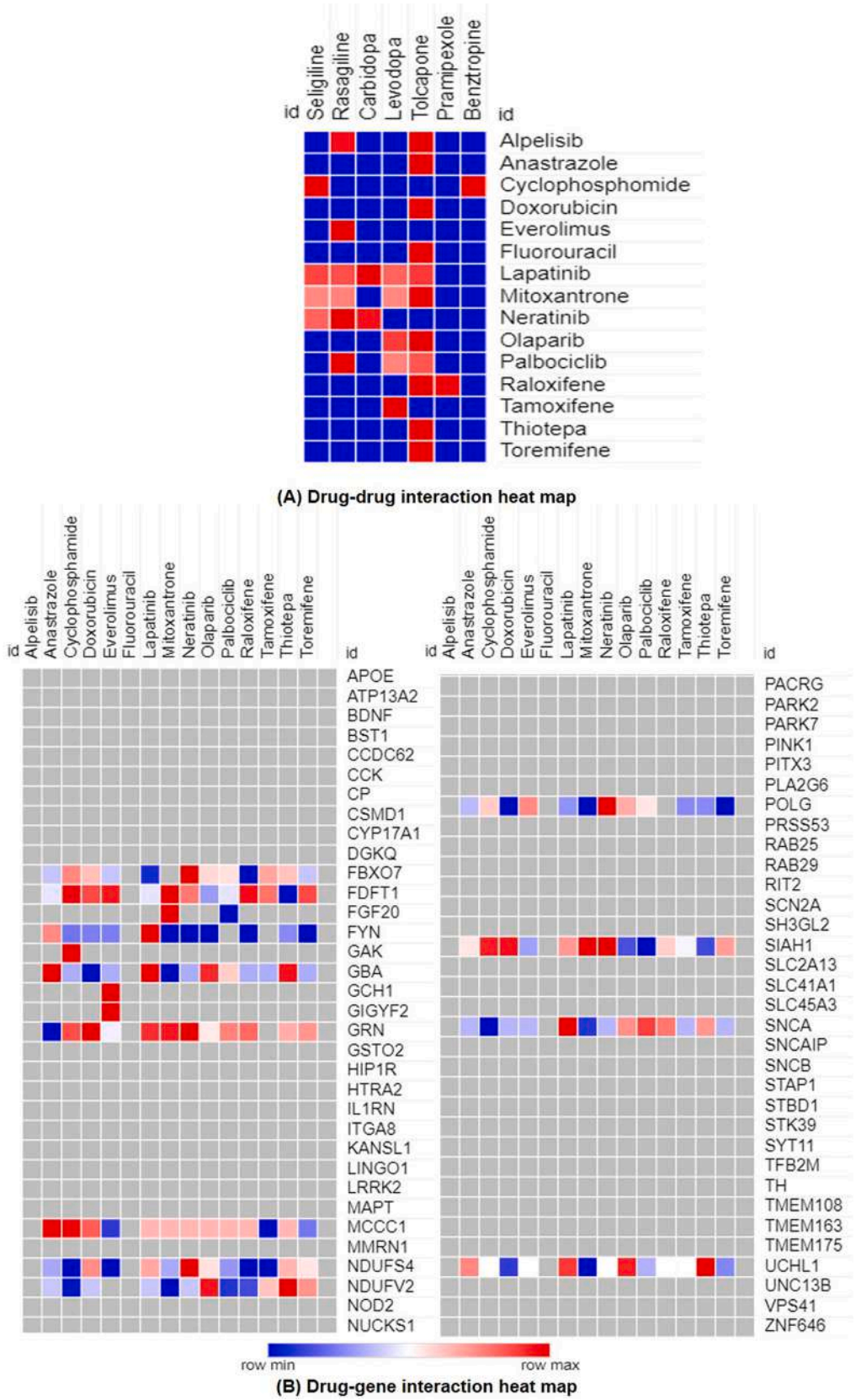


Fig. 6. (A) LINCS L1000 derived top breast cancer-related drugs mimicking the gene expression profiles of Parkinson's disease-related drugs. Red color represents correlation, and blue color represents no correlation. (B) Connectivity map analysis of breast cancer drugs with PD-related gene expression signatures. Red color represents positive correlation, and blue color represents negative correlation. Alpelisib and Fluorouracil have shown no interaction with PD-related gene expression signatures. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

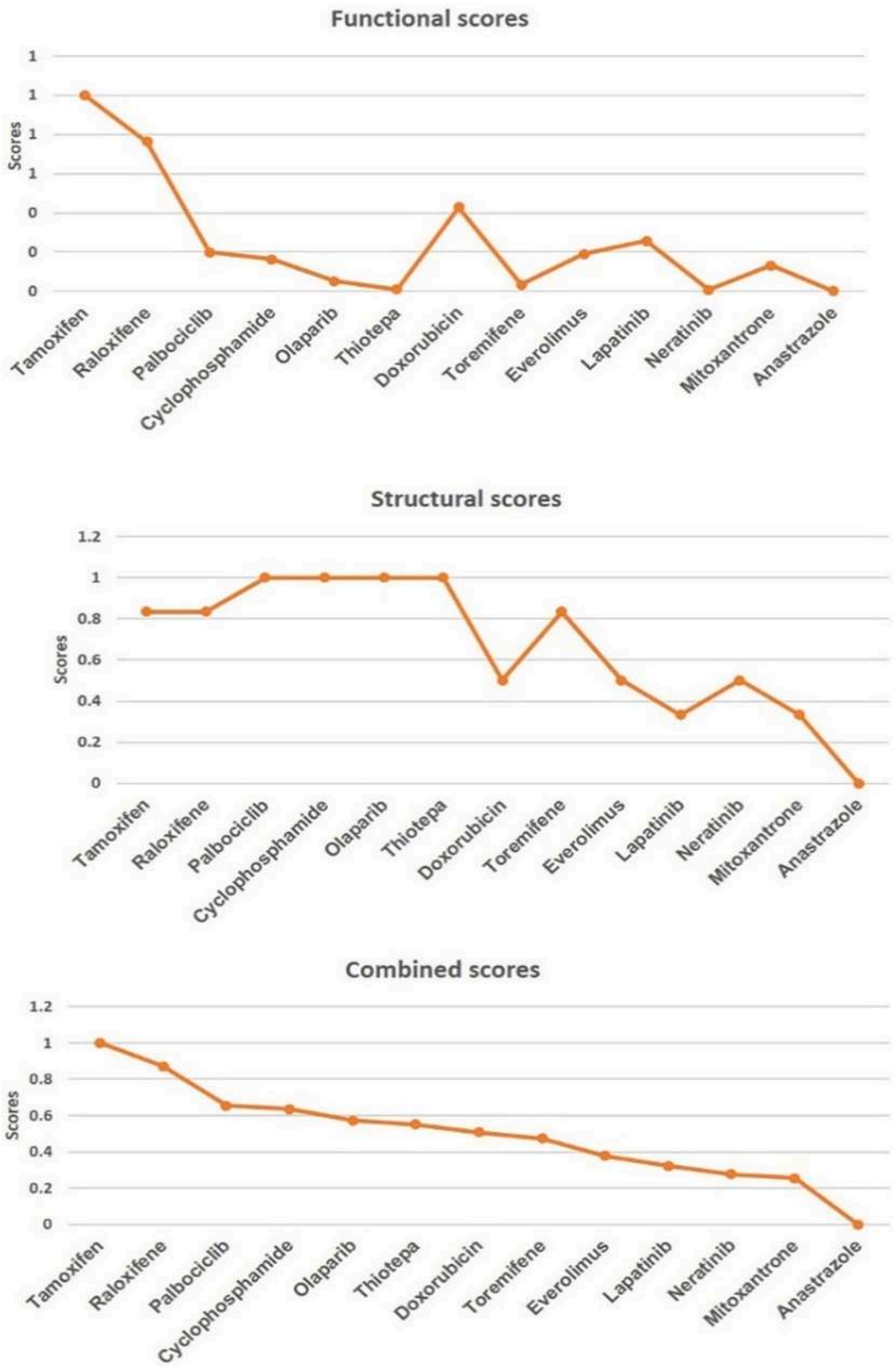


Fig. 7. Computational drug repurposing score (CoDReS) analysis of drugs. The structural scores of the drugs are more or less similar while the functional scores have shown variations. The drugs were given ranks based on their combined scores. The combined scores range from 0 to 1. Anastrazole has functional, structural and combined scores of 0. The comparative scores are presented on the Y-axis.

activation of EMT-like transition accompanied with trastuzumab resistance in HER2-overexpressing breast cancer cells (Wu et al., 2012). Upstream binding transcription factor (UBTF) is a protein involved in ribosomal RNA transcription. The exact role of UBTF in PD pathogenesis is unknown, but a study has demonstrated reduced expressions of UBTF in later stages of PD progression in substantia nigra (Garcia-Esparcia et al., 2015). Comparably, UBTF gene expression is known to be associated with breast cancer prognosis (Zhao et al., 2021).

Different enrichment analysis methods have been used to establish a connection of dysregulated pathways between PD and BRCA. We identified electron transport chain (ETC), oxidative phosphorylation and pathways of neurodegeneration as the most commonly dysregulated pathways from KEGG, Bioplanet and Wiki pathway analysis. Downstream analysis has identified ND1, ND2, ND3, ND4, ND5, ND6, NDUFA1, NDUFA2, COX1, COX2, COX3, CYTB, ATP6, and ATP8 were the most frequently appeared genes in the identified dysregulated pathways. Numerous studies have highlighted the role of defective ETC components in PD pathogenesis. The defects in mitochondrial complex I are associated with neuronal apoptosis and are involved in reactive oxygen species (ROS) generation (Blesa et al., 2015). Not long ago, a study has addressed the need of developing effective mitochondria-targeting therapies for PD as many aspects of mitochondrial functions including mitochondrial biogenesis are known as potential targets for PD treatment (Prasuhn et al., 2021). A study published Aberrations in mitochondrial complex I activity is known to induce breast tumor aggressiveness, and therapeutic enhancement of the activity inhibits disease progression. The altered activity of oxidative phosphorylation (OXPHOS) components and mutations in mtDNA and nuclear genes encoding OXPHOS subunits have been associated with PD pathogenesis (López-Gallardo et al., 2011). Studies have indicated that OXPHOS is upregulated in BRCA cells and OXPHOS inhibitors can be used as therapeutic agents in BRCA (Ashton et al., 2018). A recent study based on genetic and transcriptomic data has also revealed that mitochondria-related processes such as OXPHOS and ATP synthesis are frequently enriched pathways for genes related to AD, PD, and cancer (Forés-martos et al., 2021). Additionally, an interesting study by Valle et al. identified that oxidative phosphorylation is plays a significant role in differnet comorbidities including AD, lung cancer and glioblastoma (Sánchez-Valle et al., 2017).

To further establish the connection of PD and BRCA, we identified the regulatory signatures (TFs and miRNAs) associated with both pathologies. Among the top interacting TFs, GATA2 (GATA-binding factor 2) is reported to be highly expressed in substania nigra and regulates the expression of SNCA gene in human dopaminergic cells. Similarly, GATA2 has been documented as a tumor suppressor gene in hypoxia-mediated BRCA cell survival and tumorigenesis. In a study, nuclear factor I—C (NFI-C) is reported to be a crucial transcriptional signature in PD (Faruqui et al., 2021). In the same way, this TF is known to be involved in the NFI-C-KLF4-E-cadherin pathway to assist breast cancer tumorigenesis (Lee et al., 2015). Another TF, NF-κB (Nuclear factor κB), a proinflammatory TF, is known to be associated with dopaminergic neurotoxicity by inducing the production of inflammatory mediators (Flood et al., 2011). The role of NF-κB in BRCA pathogenesis is well established as the TF facilitates the development and progression of hormone-independent, invasive breast cancers (Wang et al., 2015). Among the top interacting miRNAs, hsa-mir-93-5p and hsa-mir-1-3p have no role reported in PD pathogenesis, however, hsa-mir-93-5p is involved in epithelial-mesenchymal transition (EMT) in BRCA (Xiang et al., 2017), and hsa-mir-1-3p is documented to regulate BRCA cell progression and metastasis (Tao et al., 2021). hsa-mir-106a-5p has been reported to be involved in cognitive improvement in PD brains (Da Silva et al., 2021). hsa-mir-106a-5p is known as a potential biomarker for predicting chemotherapy response and disease prognosis in BRCA (Chen et al., 2019).

To dissect the potential role of different therapeutics approved for both the comorbidities, we analyzed the differential gene expression signatures of the approved drugs and compared their concordance scores. Several drugs approved for BRCA were found to produce same expression signatures as PD-related drugs. We found lapatinib, mitoxantrone, neratinib and palbociclib as the top interacting BRCA drugs that have shown positive correlations with the PD drugs. To further elucidate the therapeutic efficacy of these drugs as repurposed drugs for PD, we observed how these drugs mimic or reverse the transcriptomic signatures of PD. The drugs negatively related to PD were considered as possible repurposing drugs. For instance, NDUFV2 was negatively correlated with four BRCA drugs-cyclophosphamide, mitoxantrone, palbocilcib and raloxifene. Several studies have documented the role of NADH dehydrogenase ubiquinone flavoprotein 2 (NDUFV2) gene in PD pathogenesis and the mutations in this gene are responsible for complex I deficiency in PD (Nishioka et al., 2010). The ubiquitin carboxy-terminal hydrolase L1 (UCHL1) gene, a deubiquitinase, is considered as a susceptibility gene for PD (Maraganore et al., 2004) and we found three BRCA drugs- doxorubicin, palbociclib and toremifene were able to reverse the effects of UCHL1. Similarly, mammalian seven in absentia homologue-1 (SIAH-1), a RING-type E3 ubiquitin-protein ligase is reported to promote alpha-synuclein aggregation and its ubiquitination (Lee et al., 2008). We found three BRCA drugs-olaparib, palbociclib and thiotepa were inversely correlated with SIAH1. Some studies have highlighted the role of an intron variant of methylcrotonyl-CoA carboxylase 1 (alpha) (MCCC1) gene in sporadic PD pathogenesis (Redenšek et al., 2017). Our Cmap analysis reported three BRCA drugs-everolimus, tamoxifene and toremifene were negatively correlated with MCCC1 gene. Furthermore, two BRCA drugs- Lapatinib and Raloxifene were negatively correlated with F-box domain–containing protein (FBXO7) gene that has been known to play a crucial role in parkin-mediated mitophagy and mitochondrial maintenance (Burchell et al., 2013). We reported olaparib and thiotepa were inversely related to Farnesyl-diphosphate farnesyltransferase 1 (FDFT1) gene. The exact role of FDFT1 in PD and BRCA parthogenesis is not well known but the gene has been found to promote tumor progression by assisting cholesterol biosynthesis (Kuzu et al., 2016). Mutations in the gene glucocerebrocidase (GBA) gene are considered as an important risk factor in idiopathic PD and the gene affects three pathological pathways alpha-synuclein aggregation, endoplasmic reticulum stress response and autophagic process. We reported two BRCA drugs- doxorubicin and mitoxantrone were inversely correlated with GBA gene signatures. We also found two BRCA drugs- cyclophosphamide and mitoxantrone were reversing SNCA gene signatures, the most critical gene linked with familial PD pathogenesis (Siddiqui et al., 2016).

To further confirm the repurposing potential of BRCA drugs for PD, we validated the repurposing potential of candidate drugs by CoDReS tool based on their structural and functional properties. The top ranked drugs tamoxifen and raloxifene from CoDReS analysis belong to selective estrogen receptor modulators (SERM) and are approved for estrogen receptor positive metastatic breast cancer and invasive breast cancer, respectively. These modulators act in a tissue specific manner as estrogen agonist or antagonist and many findings have suggested that SERMs including tamoxifen and raloxifene might exert beneficial effects in PD (Baraka et al., 2011). From literature analysis, we found that raloxifene has already shown neuroprotective effects in PD. Numerous studies have identified the role of raloxifene in reducing dopaminergic cell death in PD models and restoring dopamine levels (Veenman, 2020). However, there is no direct literature support available for the neuroprotective behaviour of tamoxifen in PD. A study by D'Astous et al. have reported that tamoxifen shows neuroprotective behaviour against methamphetamine and MPTP-induced toxicity when used without estrogen (Bourque et al., 2007). On contrary, a study has claimed that tamoxifen therapy might disrupt the neuroprotective effect of estrogen and is associated with increased risk of PD (Lai, 2018).

We proposed that both tamoxifen and raloxifene can activate different estrogen receptor dependent and independent mechanisms to provide neuroprotection including reduced neuroinflammation,

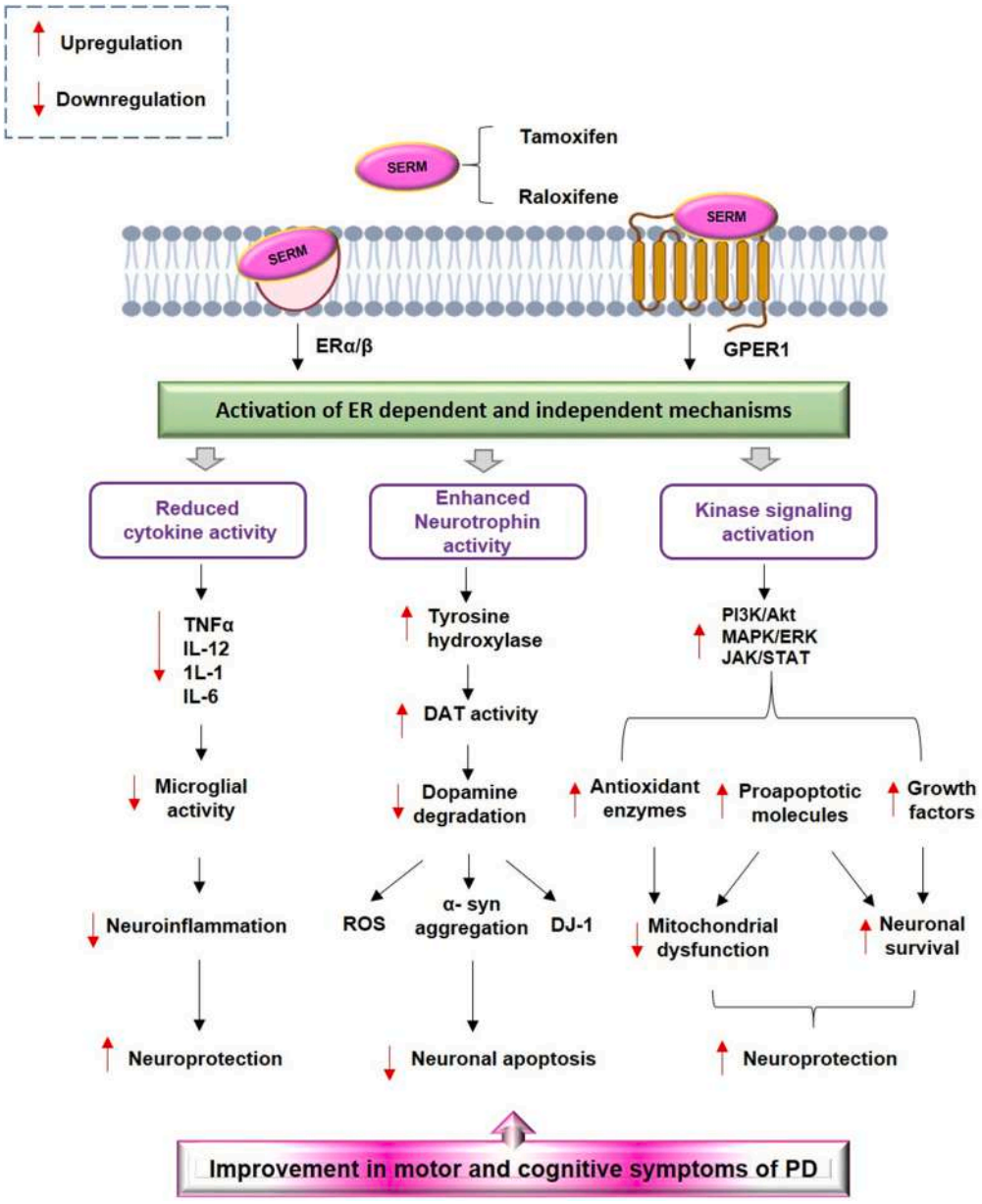


Fig. 8. Inferred mechanism of action through which selective estrogen receptor modulators (SERM) alleviate symptoms of Parkinson's disease (PD). SERMs can activate both classical estrogen receptors ERα or ERβ and nonclassical transmembrane G protein coupled ER (GPER1). Via agoinst action, SERMs activate ER independent signaling through various kinases including PI3K/Akt, MAPK/ERK or JAK/STAT kinases which provide neuroprotection by inducing expression of various antioxidant enzymes, proapoptotic molecules and growth factors required for neuronal survival. Similarly, via agonist action at ER dependent signaling SERMs modulate inflammatory cytokine levels and achieve reduced microglial activity and reduced neuroinflammation. SERMs can enhance neurotrophin activity which in turn induce the expression of tyrosine hydroxylase enzyme and dopamine transporter (DAT) activity. The elevated levels of dopamine can facilitate survival of dopaminergic neurons and alleviate oxidative stress generated by reactive oxygen species and alpha-synuclein aggregation. Red arrows indicate increase (upward) or decrease (downward) in the magnitude of response by SERMs. These pathways can reduce the symptoms related to PD and thus provide neuroprotection. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

enhanced dopaminergic signaling and reduce neuronal apoptosis. The proposed mechanism of action is summarized in Fig. 8. To conclude, our study is the first to establish a common crosstalk between PD and BRCA based on multi-omics analysis. Our findings will provide a mechanistic platform for better understanding of the molecular link between PD and cancer. We also proposed repurposing of SERM drugs for PD treatment; however, experimental studies are warranted to justify their repurposing potential.

Author's contribution

Dia Advani: Methodology, Writing- Original draft preparation, Data curation. **Pravir Kumar**: Conceptualization, Supervision, Writing-Reviewing and Editing.

Declaration of Competing Interest

All authors have read the manuscript and declared no conflict or competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.npep.2022.102283.

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Review

Protective role of anticancer drugs in neurodegenerative disorders: A drug repurposing approach

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ABSTRACT

The disease heterogeneity and little therapeutic progress in neurodegenerative diseases justify the need for novel and effective drug discovery approaches. Drug repurposing is an emerging approach that reinvigorates the classical drug discovery method by divulging new therapeutic uses of existing drugs. The common biological background and inverse tuning between cancer and neurodegeneration give weight to the conceptualization of repurposing of anticancer drugs as novel therapeutics. Many studies are available in the literature, which highlights the success story of anticancer drugs as repurposed therapeutics. Among them, kinase inhibitors, developed for various oncology indications evinced notable neuroprotective effects in neurodegenerative diseases. In this review, we shed light on the salient role of multiple protein kinases in neurodegenerative disorders. We also proposed a feasible explanation of the action of kinase inhibitors in neurodegenerative disorders with more attention towards neurodegenerative disorders. The problem of neurotoxicity associated with some anticancer drugs is also highlighted. Our review encourages further research to better encode the hidden potential of anticancer drugs with the aim of developing prospective repurposed drugs with no toxicity for neurodegenerative disorders.

1. Introduction

Neurodegenerative (NDDs) disorders are one of the most alarming medical illnesses affecting the brain and nervous system. The lack of understanding of the disease leading mechanisms makes the treatment options unavailable. Currently, an estimated 35.6 million people are surviving with Dementia, and the number is presumed to be triple by the next 30 years (Savva et al., 2019). According to the report of the World Health Organization (WHO), in the next 20 years, NDDs affecting motor functions will be the second most widespread reason for human death (Durães et al., 2018). Continuous failure of drugs designed for treating NDDs demands to develop new treatment options with maximum success rates. The discovery and development of novel drugs are a long and expensive process having a low success rate, with 70% of projects failing between phase 2 and phase 3 of clinical trials (Mottini et al., 2019). Numerous lead compounds are not developed enough to tap their potential to the maximum due to lack of funds or time (Kumar et al., 2019) Drug repurposing, drug reprofiling, or drug repositioning is a productive method to use already approved drugs for a different condition but with some common mechanism of action. This approach has been successful in many conditions like cardiovascular diseases, obesity, Parkinson's disease, cancer, irritable bowel syndrome, and psychosis (Kumar et al., 2017). The main advantage of drug repositioning is that the pharmacokinetic properties and toxicology of the candidate drugs have already been established. This hastens the process of drug development and reduces cost factors. There are two main approaches to repurposing. The first approach is to look over the drugs for new therapeutic purposes within the mechanism for which they are approved. The second, more futuristic approach is to recognize new remedial targets of the existing drugs. Some repurposed drugs entered clinical trials for NDDs specifically for AD. Anticancer, antimicrobial, antidiabetic, antihypertensive, anti-asthmatic, and antipsychotic drugs have shown promising results as AD therapeutics (Appleby et al., 2013). Advancement in machine learning and artificial intelligence (especially deep learning) has given

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new insights into understanding the binding of drugs to targets and the relation between their physicochemical properties and phenotypic changes (Issa et al., 2020).

Aging is the biggest risk factor of an array of diseases, from cancer to neurodegenerative diseases. These age-related diseases can be categorized into two groups; for instance, loss-of-function diseases like neurodegenerative disease are represented by loss of cells, tissues, or optimal physiological functions. However, gain-of-function diseases like cancer exhibit gain of cells and, sometimes, new cellular functions (Campisi et al., 2011). Several biological and pathological mechanisms confirm the connection between neurodegeneration and oncogenesis. Cancer and neurodegeneration are considered as two opposite sides of a flipping coin with some shared tuning. Although the general biology of both the diseases is opposite to each other, many genes and signaling pathways are affected in the same way in both the disorders. Cancer cells are capable of uncontrolled cell proliferation, while neurons face premature cell death. A growing body of literature is available to support the fact that the frequently mutated genes in different NDDs have some link with genes associated with cancer. p53, the most commonly mutated gene in a different type of cancers, has also shown its neuroprotective functions (Lanni et al., 2012). The expression of p53 is downregulated in various cancers but has found to be upregulated in Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) (Bae et al., 2005; Bretaud et al., 2007; Checler and Alves Da Costa, 2014; Hooper et al., 2007). Epidemiological studies conclude that the diagnosis and treatment of one disease may influence the chances of another condition. Both AD and PD are less common in cancer patients. On the contrary, cancer patients have more risk of certain age-related or other NDDs (Ganguli, 2015). The major signaling pathways investigated in cancer pathogenesis have remarkable links with neurodegenerative diseases (Ariga, 2015).

The interesting connection between cancer and neurodegeneration opens up new possibilities for the repurposing of oncology drugs for neuroprotection, albeit some limitations. Many are already in clinical trials, and some are in experimental phases. Kinase inhibitors are the most significant among anticancer agents having their proven therapeutic action in NDDs as well. Protein kinases are the diverse group of enzymes that cause the transfer of a phosphate (PO_4^-) group from Adenosine triphosphate (ATP) to the freely available hydroxyl (OH^-) group of the amino acid. Most of the kinases known to date are related to oncogenic processes. Still, they also have an essential role in neurodegeneration associated pathways like protein phosphorylation, apoptosis, or cellular stress response (Cuny, 2009; Kim et al., 2016; Salado et al., 2014; Savage and Gingrich, 2009; West, 2017).

This review summarizes the shared relationship between cancer and neurodegeneration. The inter-dependent regulation of brain cancers and neurodegeneration is discussed. The review highlights different anticancer drugs and their mechanisms, which showed encouraging results as repurposed agents in the primary neurodegenerative conditions-Alzheimer's, Parkinson's, Amyotrophic Lateral Sclerosis (ALS), Huntington's disease and Multiple Sclerosis (MS). The role of anticancer kinase inhibitors in neuroprotection has been highlighted with a particular focus on Abelson tyrosine kinase (c-Abl) inhibitors. The challenges in drug repurposing of anticancer drugs such as neurotoxicity, brain resistance, and their unknown mechanisms, are also addressed.

2. Molecular crosstalk between cancer and neurodegeneration

The molecular genetics and biological evidence support the fact that a remarkable overlap exists between neurodegeneration and cancer. Out of the two significant connections between cancer and neurodegeneration, the one is the shared biological signaling pathways, and the other are the epidemiology of both the diseases. The frequently mutated genes associated with different NDDs show a significant connection with oncology genes as summarized in Table 1.

The most considerably studied cancer-related gene p53 correlates with genes linked with AD, PD, and other NDDs (Lanni et al., 2012), as shown in Fig. 1. Activation of p53 was found to be an astounding molecular feature of NDDs. In the case of Alzheimer's, Amyloid precursor protein (APP) expression is controlled by p53 (Cuesta et al., 2008). The C- terminal intracellular fragment of APP is known to stimulate the promoter activity of p53 gene promoting tau phosphorylation. Under cellular stress, Mouse double minute 2 homolog (MDM2) levels are low accompanied by increased levels of p53 and Glycogen synthase kinase 3β (GSK3β), which phosphorylates tau (Proctor and Gray, 2010). An interesting crosstalk exists between p53 and Presenilin (PS) isoforms. P53 expression decreases by PS1, and overexpressed PS2 increase p53 expression (Checler and Dunys, 2012; Ma et al., 2009; Roperch et al., 1998). The Parkinson's associated genes parkin, PTEN-induced kinase 1 (PINK1), and Protein deglycase (DJ1) have an essential role in cancer signaling. The expression of PARKIN is downregulated in many cancer types, and it plays a vital role in regulating different hallmarks of cancer-apoptosis, mitochondrial dysfunction, and inflammation (Bernardini et al., 2017; Liu et al., 2018; Wahabi et al., 2018). It assists cancer cell proliferation by activating the Akt pathway (Gupta et al., 2017) and by maintaining the stability of G1/S cyclins (Gong et al., 2014). PARKIN negatively regulates the activity of the p53 gene in human PD brains and exerts its neuroprotective effects (da Costa et al., 2009). Like PARKIN, DJ1 expression is also found to be upregulated in many cancers (Xu et al., 2016). The gene plays a functional oncogenic role by promoting the Phosphoinositide-3-kinase-protein kinase B/Akt (PI3K-PKB/Akt) signaling pathway (Lin et al., 2018). Another PD linked gene PINK1 exerts its tumor-promoting activities dependently or independently of parkin (O'Flanagan et al., 2016; O'Flanagan and O'Neill, 2014). PINK1 sustains cellular proliferation by regulating cell cycle through G2/M and G0/G1 checkpoints (O'Flanagan et al., 2015).

The molecular association between p53 and other NDDs is not as significant as AD and PD. It has been found that ALS associated gene Superoxide dismutase (SOD1) is overexpressed in cancers and plays a vital role in maintaining cellular reactive oxygen species (ROS) levels (Li et al., 2019; Papa et al., 2014) Under mitochondrial stress conditions, SOD1 expression gets increased to activate the mitochondrial unfolded protein response (UPR) in both ALS and cancer (Gomez and Germain, 2019b). A study described the role of mutant SOD1 in p53 upregulation (Martin, 2000). The same episode of p53 alteration was observed in HD. A study pinpoints that the deletion of p53 debilitates Mutant Huntingtin (mHtt) expression associated traits like mitochondrial dysfunction in p53−/− mice (Bae et al., 2005; Ryan et al., 2006). Reverse transcriptase-polymerase chain reaction (RT-PCR) and microarray results confirmed the higher activity of p53 in ALS disease model animals (Eve et al., 2007). Like biological shreds of evidence, epidemiological studies also provide remarkable mechanistic to understand the heterogeneity of complex mechanisms that exist between cancer and neurodegeneration.

A study by Sweden's registry focusing on 19000 cases of 18 different types of cancers reported a reduced risk of dementia in cancer patients (Attner et al., 2010). Research by Framingham Heart Study Center disclosed a reduced risk of AD in sufferers of 'smoking-related cancers" and a reduced risk of cancers in AD survivors (Driver et al., 2012). A study was conducted based on the information available by the Korean National Health Insurance Services (KNHIS) for analysis of the association between AD and cancer. The data revealed that the risk of different cancers of the digestive tract, lung, and prostate cancer was significantly reduced for AD patients (Lee et al., 2018). A literature-based survey was conducted to study all the epidemiological works for cancer and central nervous system (CNS) disorders. Cancer risk was found to be significantly lower in PD cases except for melanoma, breast cancer, and brain cancers (Catalá-López et al., 2014). A concluding work was done on all the available reports on PD and cancer from 1968 to 2009, with 107,598 PD patients. The risk of smoking and nonsmoking related cancers was reported to be low in PD patients, excluding skin tumors (Bajaj et al.,

Table 1
Interrelationship between the commonly mutated genes in cancer and NDDs.

Protein	Role in cancer	Role in NDDs	References
P^{53}	Tumor suppressor	Downregulation of PS1, upregulation of GSK3β and tau phosphorylation	(Proctor and Gray, 2010; Roperch et al., 1998; Zilfou and Lowe, 2009)
PTEN	Tumor suppressor	Regulation of tau phosphorylation, Neuroprotectant for a dopaminergic system in PD, involved in DNA repair, decreased expression in ALS neurons	(Domanskyi et al., 2011; Goberdhan and Wilson, 2003; Kirby et al., 2011; Ogino et al., 2016)
ATM	Tumor suppressor. Mutated in many cancer types	ATM mutations cause Ataxia Telangiectasia. ATM inactivation causes cerebellar neuronal loss, Reduced activity in AD brains	(Choi et al., 2016; Herrup et al., 2013; Shen et al., 2016)
mTOR	Autophagy has a bipolar nature. Both tumor suppressive and oncogenic	Inhibition of autophagy	(Crino, 2016; Paquette et al., 2018)
Tau	Down expression in certain tumors	The major component of neurofibrillary tangles in AD, co-aggregation with α-synuclein in PD	(Iqbal et al., 2010; Rossi et al., 2018; Zhang et al., 2018)
APP	Increased non-amyloid genic processing of APP	Increased amyloid genic processing of APP in AD	(Kucheryavykh et al., 2019; Lim et al., 2014; Zhou et al., 2011)
Presenilin	PS1 leads to tumor invasion, and metastasis in cancer, Loss of function of PS2 promotes lung cancer development, regulation of PTEN	Presenilin constitutes the catalytic core of the γ- secretase complex. Aids in APP processing	(Li et al., 2016; Zhang et al., 2008, 2013)
CDK5	Associated with tumor proliferation, angiogenesis, chemotherapy resistance, and antitumor immunity	Causes AD-related pathophysiology hyperphosphorylation of tau and APP	(Kimura et al., 2014; Kolla et al., 2014; Liu et al., 2016; Pozo and Bibb, 2016; Shah and Lahiri, 2014)
Pin 1	Overexpressed, Induction of multiple oncogenic pathways	Downregulated in AD. Aids in tau dephosphorylation. regulates APP processing	(Chen et al., 2018; Pastorino et al., 2006; Xu et al., 2017; Yeh and Means, 2007; Zhou and Lu, 2016)
PARKIN	Downregulated in many cancers, sustain cell proliferation, Stabilize G1/S phase cyclins Promote angiogenesis	The mutation associated with autosomal recessive PD	(Dawson and Dawson, 2010; Liu et al., 2018; Wahabi et al., 2018)
PINK1	Stabilize G2/M and Go/G1 checkpoints and assist in tumor growth	Mutated in familial PD	(Jones, 2010; O'Flanagan et al., 2015; O'Flanagan and O'Neill, 2014)
DJ1	A tumor promoter, the attenuator of p53 expression	Loss of function mutation leads to Familial PD, provides neuroprotection in HD	(Ariga et al., 2013; Cao et al., 2015; Sajjad et al., 2014)
HTT	Increases p53 expression	Mutation in CAG repeat within the Htt gene leads to HD	(W. J. Huang et al., 2016; Thion and Humbert, 2018)
SOD1	Overexpressed in many cancers, induces mitochondrial unfolded protein response (UPR)	Mutation in Superoxide dismutase1 (SOD1) (an antioxidant enzyme) causes Familial ALS	(Gomez and Germain, 2019a; Pansarasa et al., 2018)
α-synuclein	Expressed in various types of tumors	Misfolded and aggregated in PD. The main component of Lewy bodies and Lewy neurites	(Israeli et al., 2011; Xu and Pu, 2016)
LRRK2	Increased risk of cancer in PD patients with LRRK2 G2019S mutations	Genetic risk factor for familial and sporadic PD	(Rui et al., 2018; Saunders-Pullman et al., 2010)
ATP13A2 (PARK9)	Overexpressed in lung tumor tissue	Downregulation or loss of function mutations result in misfolding and accumulation of α-synuclein	(Bento et al., 2016; Liu et al., 2015)
PLA2G6	Identified as a risk factor for melanoma	Mutations cause PLAN that is classified into four subtypes: ANAD, INAD, adult-onset dystonia-Parkinsonism, and AREP.	(Guo et al., 2018; Kvaskoff et al., 2011)
TSC1/2	Tumor suppressor	Inhibits mTOR activity	(Olney et al., 2017; Parry et al., 2000)
UCHL1	Tumor suppressor, promotes p53 signaling	Downregulated in AD and PD	(Choi et al., 2004; Li et al., 2010)
CDK4	Increased expression in various human cancers	Increased expression in AD brains	(Baker and Reddy, 2012; McShea et al., 1997)
CDKN2A ($p14^{ARF}$)	Tumor suppressor	Associated with cognitive decline	(Ko et al., 2018; Lye et al., 2019)
MC1R	Overexpressed in a large number of human melanomas	Neuroprotective in the nigrostriatal dopaminergic system and neuroinflammatory disease models	(Chen et al., 2017; Mykicki et al., 2016; Rosenkranz et al., 2013)
TYR	Loss of activity increases skin cancer susceptibility	Associated with Parkinson's and other neurodegenerative diseases	(Nithitanakool et al., 2009; Saran et al., 2004)

Abbreviations: PTEN: Phosphatase and tensin homolog; GSK3β:Glycogen synthase kinase 3 beta; PS: Presenilin; mTOR: The mammalian target of rapamycin; ATM: Ataxia telangiectasia mutated; CDK5:Cyclin-dependent kinase 5; PINK1: PTEN induced kinase 1; DJ1:Protein deglycase; HTT:Huntingtin; SOD1:Superoxide dismutase 1; LRRK2:Leucine rich repeat kinase 2; ATP13A2:ATPase Cation Transporting 13A2; PLA2G6:Phospholipase A2 Group VI; PLAN:PLA2G6-associated neurodegeneration; ANAD: Atypical neuroaxonal dystrophy; INAD: Infantile neuroaxonal dystrophy; AREP:Autosomal recessive early-onset parkinsonism; TSC1/2: Tuberous sclerosis protein; UCHL1:Ubiquitin carboxyl-terminal esterase L1; CDK4: Cyclin dependent kinase; 4; CDKN2A:Cyclin-dependent kinase inhibitor 2A; MC1R:Melanocortin 1 receptor; TYR: Tyrosinase (oculocutaneous albinism IA).

2010).

The epidemiological proofs validating the relatedness of cancer and other NDDs are less. A team of Swedish researchers reported a lower risk of cancer in patients with Huntington's disease and other rare NDDs as polyglutamine (Poly Q) disease. A piece of exciting news was published in the European Molecular Biology Organization (EMBO) reports that repeating small interfering RNA (siRNA) sequence, a characteristic feature of HD is a 'Super Assassin' molecule to fight cancer cells. An observational report based on the Utah population database reveals

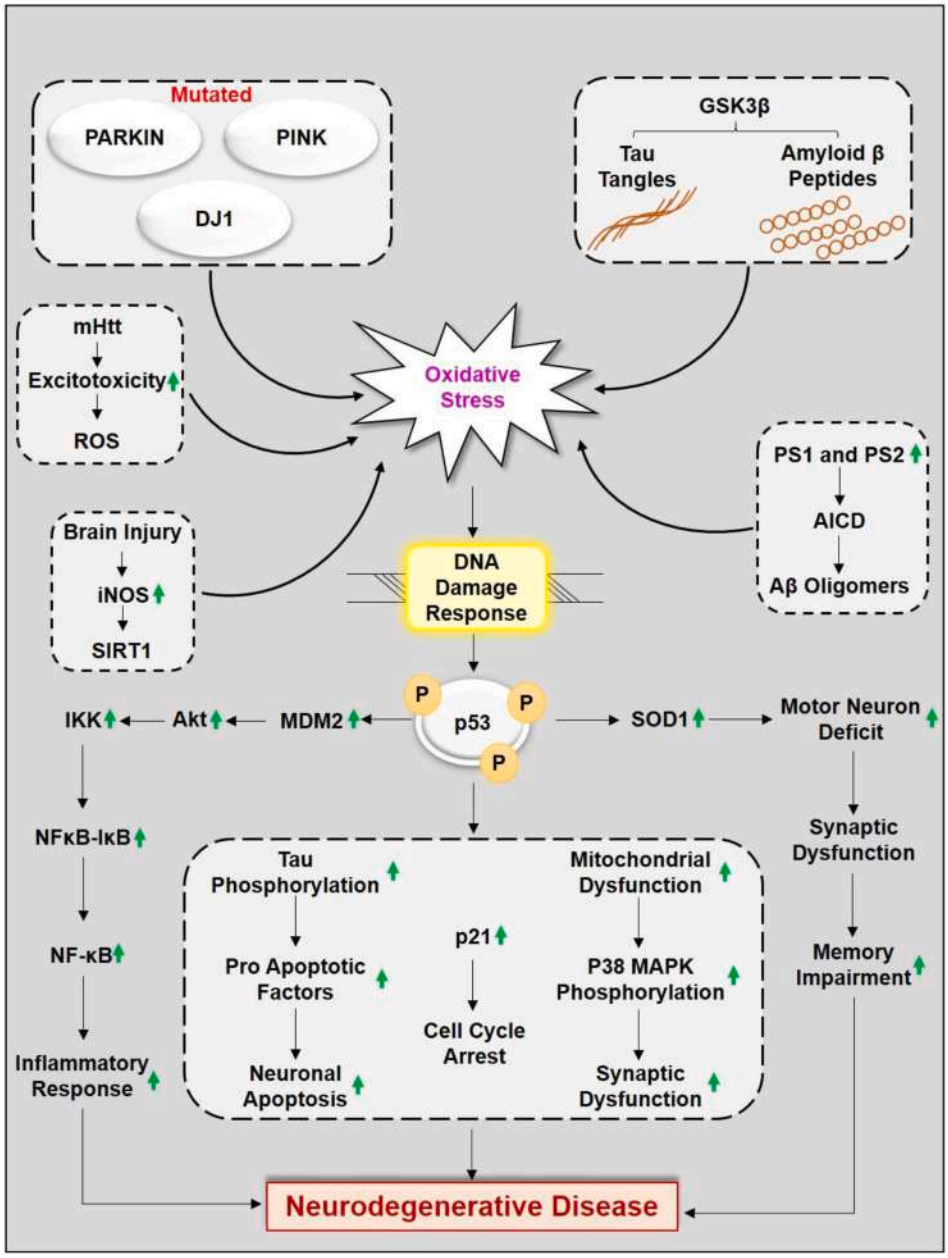

Fig. 1. The central role of p53 in cancer and neurodegeneration: p53 is an important regulator of cell survival, proliferation, apoptosis, and transcriptional regulation involved in the pathogenesis of life-threatening diseases such as cancer and neurodegenerative disorders. Increased oxidative stress activates DNA damage response, which initiates phosphorylation of p53, which causes neuronal apoptosis, synaptic dysfunction, memory impairment, neuroinflammation, and learning deficits. In AD, increased expression of Presenilin-1 and Presenilin-2 (PS1 and PS2) causes the generation of β-Amyloid induced toxicity, which results in increased oxidative stress. Amyloid-beta and tau also contribute to oxidative stress. In the case of PD, Parkin, PTEN-induced kinase1 (PINK1), and DJ1 mutations generate oxidative stress conditions. Huntingtin protein also contributes to ROS generation in the case of HD. All the oxidative stress conditions generate DNA damage response and activation of p53. Hyperphosphorylated p53 increases expression of pro-apoptotic factors, NF-κβ, and P38 MAPK, which results in neurodegeneration mediated through neuronal apoptosis, inflammatory response, and synaptic dysfunction, respectively.

different risk levels linked with various cancers in ALS patients. A decreased risk was observed for lung cancer, an increased risk for salivary and testicular tumors, and irrelevant risk for melanoma (Gibson et al., 2016). Significantly reduced cancer risk is seen with Multiple Sclerosis also. Except for brain tumors and urinary organ cancers, the chance of cancer occurrence was found to be less in MS patients (Bahmanyar et al., 2009).

3. Overlapping signaling pathways in cancer and neurodegenerative disorders

3.1. Cell cycle

The cell cycle is a fundamental cellular process typically divided into four phases: Gap 1 (G1) phase, DNA replication (S) phase, gap 2 (G2) phase and lastly cell division (M) phase. The cell cycle is tightly regulated by a series of proteins-the cyclins and the associated cyclin-dependent kinases (cdks) (Pines, 1995). Cancer is the result of abnormal cell cycle events, characterized by mutations in genes encoding cell cycle proteins or in genes regulating upstream pathways (Otto and Sicinski, 2017). On the contrary, the premature neurons, once differentiated, remain in a quiescent state for the rest of their lives. Under stress conditions, the adult neurons re-enter into the cell cycle, and this results in severe consequences such as cell death and neurodegeneration (Bonda et al., 2010). Many pieces of evidence have suggested the predominant role of cell cycle malfunctions in various NDDs. The key genes, AβPP, Presenilin 1, and Presenilin 2 (PS1/2) involved in the pathogenesis of AD, are considered as the role players in cell cycle control. In PD, dopaminergic neurons enter the cell cycle but arrest at metaphase, resulting in neuronal apoptosis.

Additionally, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated rat neuronal cultures have shown altered expression of proteins required for the G1-M phase transition (Wang et al., 2009). Likewise, ALS associated mutated SOD1 has found to be associated with reduced cell growth, destructive cytoskeletal organization, and aberrant G_2-M transition (Takamiya et al., 2005). It has been suggested that cell cycle

aberrations and oxidative stress interact in a complex way that would lead to neurodegeneration and cancer (Seo and Park, 2019).

3.2. Wnt pathway

The wingless-type murine-mammary tumor virus integration site (Wnt) is an essential pathway for many cellular functions mostly investigated in cancers such as embryonic development, tissue development and cellular differentiation (Jamieson et al., 2014). Wnt pathway activation supports tumor proliferation and concurrently protects against neurodegeneration (Behrens et al., 2009). The Wnt pathway is aberrantly expressed in many cancers and is downregulated in AD, PD, and HD. However, its significance in MS pathogenesis is not clear (Libro et al., 2016). The Wnt pathway has a protective role in AD pathogenesis by preventing Aβ induces neurotoxicity. The expressions of Wnt ligands and frizzled receptors are found to be downregulated in AD brains (Folke et al., 2019; Palomer et al., 2019). Dysregulated Wnt signaling is also linked with PD pathogenesis (Berwick and Harvey, 2012). The levels of β-catenin are proposed to be reduced in dopaminergic neurons (Cantuti-Castelvetri et al., 2007). A study by Godin et al. suggested that wild-type Htt gene induces β-catenin phosphorylation while a mutation in Htt leads to β-catenin accumulation (Godin et al., 2010). The altered Wnt pathway has found to be linked with the re-myelination process associated with MS.

3.3. Redox signaling pathway

Redox homeostasis plays a crucial role in cellular systems, and any alteration in the signaling processes lead to aging, neurodegeneration, and cancer. Oxidative stress and ROS supported cancer initiation by promoting DNA damage, cancer proliferation by further DNA alteration, and cancer metastasis. The neurodegenerative disorders like AD, PD, HD, and ALS are linked with oxidative damage and impaired redox mechanisms (Calabrese et al., 2009). In AD, increased oxidative stress induces β-secretase 1 (BACE1) secretion and Aβ production, which further creates oxidative stress (Guglielmotto et al., 2011). Metals like iron (Fe), copper (Cu), and zinc (Zn) contents are found to be higher in amyloid plaques as compared to the surrounding tissues (Rajendran et al., 2009). In PD, the oxidized products of dopamine generate various free radicals and disturb mitochondrial functions (Gautam and Zeevalk, 2011). The levels of different thiols like Glutathione (GSH) are reduced in the case of PD, where these species are important in maintaining redox balance (Pearce et al., 1997; Vural et al., 2017). Accumulation of Fe and dysregulated Ca^{2+} signaling also contribute to the redox imbalance in PD brains (Martin-Bastida et al., 2017; Uversky et al., 2001). In the case of ALS, mutant SOD1 is associated with increased oxidative stress. Mutant SOD1 interacts with mitochondria and lessens the reduced/oxidized glutathione (GSH/GSSG) ratio. Increased hydrogen sulfide (H_2S) levels also contribute to oxidative damage in ALS (Davoli et al., 2015).

3.4. MAPK pathway

The serine-threonine kinases Mitogen-activated protein kinases (MAPKs) regulate different cellular functions such as cell growth, differentiation, and cell death. The MAPK signaling has three major kinases: MAPK kinase kinase (MAPK3K), MAPK kinase (MAPK2K), and MAPK. The role of different MAPK kinases is widely investigated in tumor biology. Mutations in ERK kinases- B-Raf and K-Ras are frequently observed in many human cancers (Halilovic and Solit, 2008; Kim and Choi, 2010; Schubbert et al., 2007). Likewise, MAP kinases have interesting roles in neurodegeneration. In the case of AD, MAP kinases are involved in tau phosphorylation, and tau tangle formation. The mitochondrial dysfunction associated with AD is mainly driven by Extracellular signal regulated kinase (ERK), downregulation of which restores the mitochondrial abnormalities in AD (Gan et al., 2014; Kim and Choi, 2015). Under oxidative stress, activated c-Jun N-terminal kinase (JNK) and p38 induce the expression of APP processing BACE1 enzyme In PD, aggregation of α-syn induces activation of p38, E and MAPK which induce expression of different neuroinflammatory cytokines in microglial cells (Klegeris et al., 2008). The activity of JNK kinase is known to be high in dopaminergic neurons, and its function is altered by parkin (Cha et al., 2005). JNK and p38 kinases play a dominant role in the motor neurons associated abnormalities (Ackerley et al., 2004; Bendotti et al., 2004). p38 promotes ALS progression by inducing NO production in the motor neurons via Fas-associated apoptosis (Raoul et al., 2006, 2002).

3.5. Angiogenesis

Angiogenesis is a vital process for tumor cells to maintain their survival and metastasis. Tumor cells overexpress different angiogenic markers such as Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) (Rajabi and Mousa, 2017). Some recent researches identified the role of angiogenic mechanisms in neuroinflammation and neurodegeneration. One of the angiogenic inhibitors, Thalidomide and its similar compounds have shown good experimental results in AD and PD disease models (De Filippis et al., 2012). The literature has numerous studies justifying the neuroprotective role of VEGF. VEGF provides neuroprotection against excitotoxicity via two pathways: PI3K/Akt pathway and Mitogen-activated protein kinase/extracellular signal regulated kinase (MEK/ERK) pathway (Veikkola and Alitalo, 1999). VEGF and Transforming growth factor-beta (TGFβ) and Tumor necrosis factor-alpha (TNFα) are highly expressed in AD brains (Tarkowski et al., 2002). VEGF protects motor neuron death under stress conditions of excitotoxicity, SOD1 induced toxicity, and hypoxia (MATSUZAKI et al., 2002; Svensson et al., 2002). Studies have suggested that Aβ promotes angiogenesis by Notch signaling and γ secretase pathways (Jefferies et al., 2013). Interesting work was done by David and coworkers, who found increased levels of angiogenic markers in Cerebrospinal fluid (CSF) of PD patients (Munoz and Woulfe, 2015).

3.6. PI3K/AKT/mTOR pathway

The PI3K/AKT/mTOR pathway is critical for an array for cellular functions such as cell proliferation, grown, survival and metabolism. PI3K family is composed of catalytic subunits (p110α, p110β, p110δ and p110γ) and non-catalytic or regulatory subunits (p85, p87 and p101) (Kobayashi et al., 2020). The PI3K signaling is considered as the major controller of cancer. The pathway is interrupted in a wide variety of human cancers through different mechanisms such as inactivation of PTEN, mutation of PI3K, or activation of upstream elements of PI3K (Yang et al., 2019). The pathway is also essential for neuronal survival. In Alzheimer's, the PI3K pathway controls cell survival, neurogenesis, oxidative stress, Aβ metabolism, and tau phosphorylation (Kirschenbaum et al., 2001). Aβ exerts neurotoxicity by inhibition of PI3K signaling, and a PI3K activator may provide neuroprotection by activation of the PI3K pathway (O'Neill, 2013). A study proposed the role of the PI3K/AKT/mTOR pathway in Aβ25-35 induced autophagy. The mTOR signaling has a potential therapeutic aspect in the brain in the autophagic clearance of polyglutamine protein aggregates in HD (Berger et al., 2006), clearance of Aβ aggregates in AD (Spilman et al., 2010), and removal of α -syn aggregates in PD (Crews et al., 2010). A study by Mammana et al. suggested the therapeutic role of PI3K/mTOR pathways, in immunomodulation and prevention of relapses in MS (Mammana et al., 2018). The experimental studies in the MS disease model proposed that PI3K signaling has an important role in leukocyte survival (Haylock-Jacobs et al., 2011).

3.7. Cytokine and immune signaling

Cytokines are the small proteins that contribute to different cellular

functions like growth, survival, and differentiation at significantly minimal concentrations. Cytokines have both tumor-promoting and tumor degrading roles and involved in various tumor-associated processes such as angiogenesis, tumor growth, and metastasis, and immunomodulation (Dranoff, 2004). Cytokines are the mediators of cellular injury and repair in different neurodegenerative conditions. Cytokines like Interleukin-1 beta (IL-1β) and TNF causes neurotoxicity by inducing glutamate production. Another cytokine TGFβ is associated with the pathogenesis of AD, PD, HD, ALS, and MS (Hammond et al., 2019). The altered TGFβ signaling in AD contributes to Aβ aggregation, microglial activity, and neurodegeneration (Tesseur et al., 2006; Tichauer and von Bernhardi, 2012). In PD, TGFβ signaling is involved in dopaminergic neuronal survival and development. Studies identified the higher concentration of TGFβ in symptomatic and asymptomatic HD brains (Battaglia et al., 2011; Chang et al., 2015) Reports suggested that astrocytes secrete TGFβ as a neuroprotective mechanism to prevent motor neuron degeneration in ALS.

The complement system plays an important dual role in cancer having antitumor and pro-tumor activities. The complement system mediates inflammation associated with tumor progression and regulates the response of T cells for tumors (Merle et al., 2015). Complement dysregulation has a vital link with neurodegeneration as well. The aberrant activation of the complement cascade in the AD mouse model is associated with cognitive deficits and synaptic dysfunction (Hong et al., 2016). Aβ is a potent stimulator of the complement pathway, and inhibiting complement signaling helps to reduce AD-associated symptoms such as cognitive deficits and microglial activation (Litvinchuk et al., 2018). Different immune cells, including microglial cells, astrocytes, oligodendrocytes, and infiltrating immune cells, play a part in the pathology of neurodegenerative disorders.

4. Brain tumors and neurodegeneration

Solid brain tumors originating in the head, such as gliomas, the most aggressive and malignant forms of Glioblastoma multiform (Type IV) are correlated with the evolution of NDDs as summarized in Table 2. Evident studies have shown that these malignant primary brain tumors exert their action of neuronal inhibition by causing an excessive release of glutamine from the cysteine or glutamine antiporters x-CT (namely SLC7A11) (Kim et al., 2001). These further causes an increase in the level of neuronal toxicity initiates excite-toxicity leading to neuronal cell death prompting to neurodegeneration (Behrens et al., 2000; Savaskan et al., 2015; Takano et al., 2001; Ye and Sontheimer, 1999).

This shows that neurons that are in close vicinity of these malignant

Table 2
Association of various cell cycle and signaling components in neurodegeneration and brain tumors.

SN	Altered signaling, cell cycle or secretory components	Associated Subunits	Effective role in brain malignancies	implicative functions in neurodegeneration	Brain malignancies involved	References
1	PP2A	PP2A-Aα, PP2A-Aα-W257G, PP2A-B55α	Acts as tumor suppressor; Downregulation increases tumorigenicity and anchorage-independent growth,	Major phosphatases for α-synuclein and increased Aβ in AD	Oligodendrogliomas, Glioblastoma and Anaplastic Oligodendrogliomas	(Chen et al., 2005; Colella et al., 2001; Eichhorn et al., 2009; Fan et al., 2013; Ruediger et al., 2011; Sontag and Sontag, 2014)
2	Cyclin F	CDK activity not required; Binds SLBP	Upregulated in head malignancies; Inhibitors of tumorigenesis in primary gliomas	Impairment in autophagy in case of ALS and FTD	High grade Gliomas	(Deshmukh et al., 2018; Kabashi et al., 2008; Sreedharan et al., 2008; Williams et al., 2016)
3	Pin 1	Cyclin D1	Upregulated in brain malignancies; Acts as a tumor promoting factor	Loss of synapse and plasticity in AD due to Downregulation; Forms Lewy bodies in PD brain (Upregulated)	Solid brain tumor	(Bao et al., 2004; Lu et al., 1999; Yeh and Means, 2007)
4	Cyclin D1	CDK 4 and CDK 6	Overexpressed and hyper activated	Increased level of tau phosphorylation and caspace-3 activation; promotes apoptosis in AD brains	Destructive Oligodendrogliomas	(Atabay and Karabay, 2012; Malumbres and Barbacid, 2001; McShea et al., 1997; Musgrove et al., 2011; Sherr, 1994)
5	Cyclin E	USP27	Overexpressed and promotes genomic instability	Expression induces activation of cell cycle in post mitotic neurons in AD models	Glioblastoma Multiforme	(Akli et al., 2004; Casimiro et al., 2012; COPANI et al., 1999; Kitada et al., 1998; Morris et al., 2010; Schapira and Jenner, 2011; Schulz et al., 1997)
6	Glutamine antiporters xCT (SLC7A11)	Glutamate receptors	Promotes growth of gliomas cells	Promotes neuronal cell death; neurodegeneration in vicinity of malignant cells	Solid brain tumors especially gliomas	(Behrens et al., 2000; Kim et al., 2001; Ye and Sontheimer, 1999)
7	Neuroligin-3	Dis-integrin, metalloproteinase	Increased proliferation and tumor growth *in-vivo*	Induces aging and neurodegeneration	Paediatric gliomas	(Venkatesh et al., 2019, 2017, 2015)
8	TIAF1	Smad-4 and WWOX	Suppress anchorage independent growth, metastasis	Induces apoptosis and cell death promoting neurodegeneration	Primary brain tumors	(Chang et al., 2012; Chou et al., 2019; Lee et al., 2010)
9	Zinger-finger like protein	Myelin Transcription factors-1	Promotes metastasis and invasion	Binds tau and Aβ in AD brains	Malignant gliomas	(Armstrong et al., 1997; Lee et al., 2017)
10	p53	p53-R273H, p53-G245D,	Enhances metastasis, invasion during gain-of-function	Unfolded p53 and Aβ accumulation in AD brains	Neuroblastoma and high grade gliomas	(Buizza et al., 2013; Dorszewska et al., 2014; Eriksson et al., 2019; Kalo et al., 2012; Lanni et al., 2008; Lisek et al., 2018; Tanaka et al., 2018; Yeh et al., 2017)

Abbreviations: PP2A: Protein phosphatase 2; SLBP Stem-Loop Binding Protein; Pin1: Peptidylprolyl Cis/Trans Isomerase, NIMA-Interacting 1; TIAF1: TGFB1-induced anti-apoptotic factor 1.

GBMs are highly prone to degradation (Takano et al., 2001). The activity of glutamine receptors release from these glioma cells was confirmed by inducing an antagonist MK801 (also known as Memantine) that prevented the loss of neuronal activity in the vicinity of glioma cells (Lehrer, 2018, 2010). Apart from the induction of neurodegeneration by malignant brain tumor cells, some studies have also identified the role of neurons in regulating the activity of cancer cells within the brain microenvironment. Optogenetic induction of neuronal activity in a pediatric GBM xenograft model promoted proliferation and increased tumor growth *in-vivo* (Venkatesh et al., 2019, 2017, 2015). Researchers identified that this tumor growth was mediated due to the release of neuroligin-3 (synaptic adhesion molecule) from the postsynaptic neuron in an activity cleavage dependent manner. Neuroligin-3 then acts as a mitogen for these glioma cells, causing the activation of various signaling pathways such as PI3K-mTOR pathways, enhancing proliferation and growth of gliomas that further causes neuronal depletion and cell death (Venkatesh et al., 2017; Zeng et al., 2019).

Researchers have also shown the aggregation of various transforming factors between the junctional interface of these malignant glioma cells. Factors such as transforming growth factor β (TGF- β) 1-induced anti-apoptotic factors (TIAFA1) show an aggregation in the hippocampus region of AD and non-demented patients along with Smad-4 or WW domain-containing oxidoreductase (acting as tumor suppressors) and accumulated Aβ (Bhadbhade and Cheng, 2012; Chang et al., 2012). TIAFA1 aggregates then cause suppression of anchorage-independent growth, tumor progression, and finally

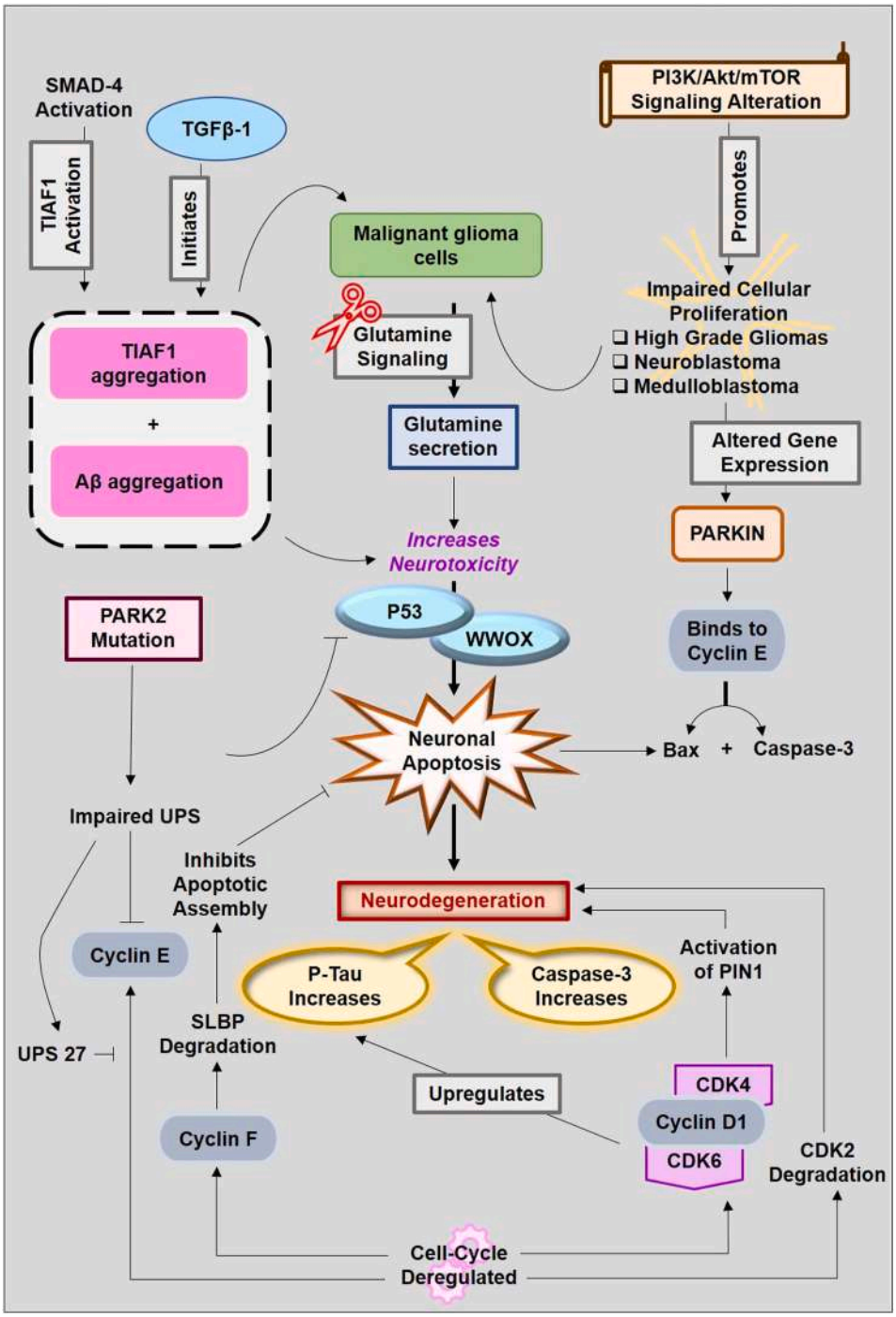

Fig. 2. Implicated role of malignant brain tumors and altered cell cycle in neurodegeneration: Altered PI3K/Akt/mTOR pathway leads to increased cellular proliferation of malignant brain tumor cells. Primary brain tumor cells lead to the release of glutamine due to impaired leads to the release of glutamine due to impaired glutamine receptors and glutamine signaling. Glutamine then further leads to increased neurotoxicity. Increased neurotoxicity leads to upregulated gene expression. Binding of tumor suppressor growth factor β 1(TGFβ-1) with TGF-β receptors promotes aggregation of TGFB1-Induced anti-apoptotic factor-1 (TIAF1). Aggregation of TIAF1 promotes tumoral edema formation in various malignant primary brain tumors. Also, the binding of amyloid-β (Aβ) with TGF-β lead to increased neurotoxicity. Increased neurotoxicity then promotes increased neurodegeneration. Binding of p53 with WW-domain containing oxidoreductase (WWOX) enhances apoptosis. Enhanced apoptosis leads to increased neurotoxicity. Meanwhile impaired ubiquitin-proteasome system (UPS) blocks p53 interaction and Cyclin-E. Regulation of TIAF-1 by mother against DPP homolog-4 (SMAD-4) also enhances neurodegeneration. Ubiquitin specific peptidase (USP-27) acts to stabilize Cyclin-E. This interaction further cause degradation of Cyclin-dependent kinase (CDK2). Cyclin D1 binding with CDK4 and CDK6 leads to activation of PIN1. PIN1 acts to regulate cancer progression negatively. Increased level of tau phosphorylation promotes neurodegeneration. Interaction of phosphorylated stem-loop binding protein (SLBP) with Cyclin-F leads to enhanced neuronal death promoting neurodegeneration.

metastasis, thereby causing neuronal cell death leading to neurodegeneration (Bhadbhade and Cheng, 2012; Lee et al., 2010). TIAF1/p53/WWOX responsible for suppressing the gliomas cell growth (Chiang et al., 2013), caused increased accumulation of brain proteins due to antagonism of p53 towards WWOX-mediated cancer suppression, therefore, leading to an increased pace of neurodegeneration. These studies show the defined role of GBMs in mediating the neuronal cells in the development of NDDs, as shown in Fig. 2.

5. Neuroprotective functions of anticancer drugs

Several studies have been conducted to identify the prospective role of different anticancer drugs for AD, PD, ALS, MS, and HD treatment as summarized in (Table 3 and Fig. 3). The following sections highlight different research works conducted in this context.

5.1. Alzheimer's disease

Studies have been conducted to identify the prospective role of different anticancer drugs for AD treatment in both *in-vitro* and *in-vivo* conditions. The two retinoid X Receptor (RXR) agonists Bexarotene and Tamibarotene exhibited neuroprotective properties. Bexarotene induces changes in expression of genes that cause cellular differentiation, reduced cell proliferation, apoptosis, and tumor growth inhibition. It has been described that orally administered Bexarotene in an AD mouse model resulted in the clearance of Amyloid-beta (Aβ) in an Apolipoprotein E (ApoE) dependent manner. The ApoE glycoprotein has the high expression in the liver and brain. Microglia and astrocytes express ApoE protein. ApoE functions as an Aβ binding protein and accelerates Aβ deposition in amyloid plaques. Bexarotene facilitates Aβ clearance by transcriptionally activating Peroxisome proliferator-activated receptor gamma-Retinoid X receptor (PPARγ-RXR) and Liver X receptor-Retinoid X receptor (LXR: RXR) and increased expression of ApoE, ATP-binding cassette transporter 1 (ABCA1) and ATP binding cassette sub-family G member 1 (ABCG1) genes (Cramer et al., 2012). In a study, Bexarotene at a concentration of 300 mg was given to two different groups: ApoE carriers and ApoE non-carriers. The drug reduced plaque burden in apoE4 non-carriers. The authors noted that the plaques in ApoE4 carriers are harder to solubilize due to compactness (Cummings et al., 2016). A study described that age-dependent critical concentration of Bexarotene could reverse brain cell damage in APP/PS1 mice (Rosenthal et al., 2016). Work on the *C. elegans* model suggested that Bexarotene interfered with the primary nucleation of Aβ-42 aggregation (Habchi et al., 2016). Tamibarotene (Am80) a retinoic acid receptor (RAR) α/β agonist approved in Japan for the treatment of Acute Promyelocytic Leukemia (APL).

Am80, a multi-target drug, maybe a potent therapeutic for AD treatment. A study on APP23 mice describes that Am80 reduces extracellular insoluble Aβ (42), but no effects were observed on the soluble Aβ levels. The decrease in extracellular Aβ may be due to increased α-secretase transcription or phagocytosis by activated microglial cells (Kawahara et al., 2009). A study on Nilotinib in mice suggested that the drug facilitates autophagy and triggers increased parkin levels thus helps to reduce Aβ and tau protein levels in AD brains. Nilotinib inhibits c-Abl tyrosine kinase and helps to stabilize parkin-beclin1 interaction that leads to autophagic clearance of Aβ and tau proteins. Work in human embryonic stem-cell-derived Alzheimer's disease models showed that Nilotinib could recover the synaptic dysfunction and increases the expression of Ras-related protein Rab-3A (RAB3A). An ongoing clinical trial is conducted at the Georgetown University in 2017 to evaluate the role of Nilotinib in the clearance of Aβ plaques and tau tangles in AD brain patients. (Lonskaya et al., 2014; Nishioka et al., 2016).. (Table 4)

Another work on 3, 6′ dithalidomide described that the drug reduced many hallmark characters of AD like tau phosphorylation, Aβ accumulation, Aβ plaque number, and memory deficits in AD mice. Treatment with both thalidomide and 3, 6-DT produced a decrease in some activated microglia cells. The activated microglial cells release toxic ROS and proteolytic enzymes to enhance the processing of APP into Aβ peptide (Tweedie et al., 2012). The National Institutes of Health (NIH) conducted a 24-weeks, double-blinded, randomized, placebo-controlled phase II clinical trial on 185 subjects with mild to moderate AD. The outcome, where the administration of thalidomide with a maximum dose of 400 mg/day reduces amyloidogenesis, but it has not been well tolerated by the patients. These results suggested that there was no significant cognitive impairment in thalidomide treated group (Decourt et al., 2017). However, Imatinib (Gleevec) reduces Aβ levels by indirect inhibition of the γ-secretase enzyme and by producing APP variants. The *in vitro* results with Imatinib were not reproducible due to its poor brain penetration (Hussain et al., 2013; Netzer et al., 2017).

Acetylcholinesterase inhibitors are the widely explored drugs developed for AD till the date. Sunitinib is an anti-cancer drug approved by the FDA for the treatment of metastatic renal cell carcinoma and Imatinib resistant gastrointestinal tumors, which showed success as an anti-Ache drug. Further, studies have suggested that Sunitinib may be a potential drug for the treatment of NDDs (Sanchez et al., 2013) whereas, two AD animal models, tg2576 and 3xTgAD mice showed that Sunitinib improves cognitive performance (Grammas et al., 2014). A study demonstrated that in the scopolamine-induced mouse model, Sunitinib decreases the activity of acetylcholine esterase (Ache). Molecular docking analysis revealed that Sunitinib interacts with the Catalytic Anion Site (CAS) and Peripheral Anion Site (PAS) of Ache (Huang et al., 2016). Moreover, it was also investigated in HIV models of neurotoxicity that Sunitinib inhibited CDK5 activity and tau hyper-phosphorylation (Wrasidlo et al., 2014).

Sunitinib is considered as an anti-angiogenic agent and can be used for AD therapeutics for neo-angiogenesis and for hyper vascularization which is associated with pathological conditions of AD. Sunitinib is able to alter the levels of Aβ secreted from endothelial cells by inhibiting VEGF signaling (Jefferies et al., 2013). Another tyrosine kinase inhibitor, Pazopanib, inhibits Ache and restored cognitive deficits to the same extent as Donepezil. A study has shown that Pazopanib reduces phosphorylated tau levels and modulates astrocytic activity in the AD mouse model (Javidnia et al., 2017; Yang et al., 2015). Further, chemotherapeutic FDA approved drug Carmustine (BCNU) is used to treat some types of brain tumors, lymphomas, myelomas, and metastatic brain tumors. BCNU is an alkylating agent responsible for DNA disruption, cell cycle arrest, and apoptosis. A study demonstrated that BCNU decreases Aβ level by altering APP trafficking and cleavage. *In vitro* and *in vivo* activity of BCNU is independent of the secretase (α, β, and ϒ) enzymes. The main advantage is that there are no side effects of Carmustine as seen with secretase inhibitors and it is also a blood-brain barrier (BBB) penetrating drug and thus, BCNU can be a favorable anti-Aβ drug (Hayes et al., 2013).

Paclitaxel (Taxol), another anti-neoplastic agent, is a microtubule inhibitor commercially available for the treatment of breast, pancreas, ovarian, lung, and cervical cancer. Paclitaxel alters the dynamic stability of microtubules by binding to the β subunit of tubulin (Brunden et al., 2011). Researches have shown that it causes inhibition of cell division and apoptosis in cancer cells. An experimental study by Angiotech Pharmaceuticals describes that paclitaxel has positive effects on movement disorders. A group led by Michaelis conducted experiments to confirm that Taxol helps to slow down the degeneration of nerve cell branching ends. Further, a study proposed that Taxol reduces Aβ toxicity by inhibition of Aβ induced activation of calpain which reduces the proteolysis of p35 to p25 and decreased activation of CDK5/p25 complex. The reduced activity of CDK5/p25 complex helps to minimize tau phosphorylation and disease progression (Li et al., 2003). The potential of Taxol as an AD therapeutic is limited due to its poor bioavailability to the brain. Brain penetrates Taxol analogs that may be useful in AD treatment.

Table 3
Neuroprotective role of different anticancer drugs in various neurodegenerative disorders.

Drug	Drug class	Role in Cancer	Pathways Involved	Role in NDDs	Type of NDDs	References
5-Fluorouracil	Antimetabolite	Inhibits DNA and RNA synthesis	DNA synthesis pathway	Improves motor activities	ALS	(Rando et al., 2019) (Longley et al., 2003)
Alemtuzumab	Monoclonal antibody	Causes CD52 cell lysis and lymphocyte depletion	Inflammatory response pathway	Immunosuppression and immunomodulation	MS	(Fraser et al., 2007) (Coles, 2013a)
Bexarotene	Retinoid X receptor agonist	Inhibits cell cycle progression, prevents multidrug resistance, inhibits angiogenesis and metastasis	p53/p73 pathway	Reduces Aβ and huntingtin levels, promote microglial phagocytosis and improves motor functions	AD, HD	(Dickey et al., 2017), (Qu and Tang, 2010)
Carmustine	Alkylating agent, DNA crosslinking agent	Tumor growth inhibitor. Inhibit DNA replication and transcription.	DNA synthesis pathway	Reduces Aβ production	AD	Hayes et al. (2013)
Cladribine	Nucleoside analog	Inhibits lymphocyte proliferation by inhibiting DNA synthesis and DNA repair	DNA synthesis pathway	Reduces circulating B and T lymphocytes, Neuroprotectant	MS	Jacobs et al. (2018)
Cyclo-phosphamide	Alkylating agent, Inhibits cell division	Inhibits nucleic acid synthesis. Induces DNA damage and base mispairing	Inflammatory response and cell cycle pathway	Immunosuppression and immunomodulation	MS	(Awad and Stue, 2009) (La Mantia et al., 2007)
Dactolisib	PI3K and mTOR inhibitor	Inhibits autophagy, interferes with DNA repair and stops the proliferation of cancer cells	PI3K/Akt/mTOR pathway	Reduced memory impairment, decreases microglial activation and lowers IL-10 levels	AD	(Bellozi et al., 2019; Brinkman et al., 2020; Ediriweera et al., 2019)
Dasatinib	Tyrosine kinase inhibitor	Inhibits the kinase signaling of Bcr-Abl and Src kinases	JAK-STAT, MAPK and PI3K-Akt pathway	Inhibits amyloid dependent microgliosis	AD	(Dhawan and Combs, 2012) (Keating, 2017)
Dabrafenib	Tyrosine kinase inhibitor	Inhibits MAPK signaling and causes cell cycle arrest	MAPK/ERK pathway	Neuroprotectant, Activates Extracellular signal regulated kinase (ERK), Inhibits c-Jun N terminal kinase (JNK/c-Jun) phosphorylation	PD	Uenaka et al. (2018)
Epothilone D	Microtubule-stabilizing agent	Stops cell cycle by binding to tubulin in cancer cells leading to apoptosis	Cell cycle	Reduced axonal dystrophy and increases axonal microtubule density improving axonal transport and cognitive function	AD	(Cheng and Huang, 2018; Zhang et al., 2012)
Erlotinib	EGFR inhibitor	Inhibits the tyrosine kinase activity of EGFR	JAK-STAT, MAPK and PI3K-Akt pathway	Improves survival in SOD1 mouse	ALS	(Le Pichon et al., 2013) (Bareschino et al., 2007)
Imatinib	Tyrosine kinase inhibitor	Inhibits leukemogenesis by targeting downstream signaling of Abl kinase	JAK-STAT, Ras/MAPK, PI3K-Akt, and Src-Pax-Fak-Rac pathway	Inhibition of γ-secretase activity, reduction of soluble SOD1	AD, ALD	(Cuny, 2009)
Lonafarnib	Farnesyl transferase inhibitor	Blocks post-translational modification of Ras and inactivates it	Rhes pathway	Activates lysosomes and decreases tau pathology	AD	(Morgillo and Lee, 2006) (Hernandez et al., 2019)
Mitoxantrone	Topoisomerase II inhibitor	Inhibits DNA synthesis and DNA repair	Inflammatory response and DNA synthesis pathway	Immunosuppression and immunomodulation, Improves neurological disability	MS	(Fox, 2004) (Martinelli Boneschi et al., 2013)
Methotrexate	Dihydrofolate reductase inhibitor	Inhibits Nucleic acid and protein synthesis	Folate pathway	Immunosuppressant, reduction in serum creatine kinase concentrations	MS	(Gray et al., 2003) (Mikkelsen and Thorn, 2011)
Nilotinib	Tyrosine kinase receptor	Anti-proliferative action by inhibiting different tyrosine kinases	JAK-STAT, MAPK and PI3K-Akt pathway	Reduction of Aβ and α-syn. Decreases parkin solubility, and restore dopamine levels	AD, PD	(Tanabe et al., 2014) (Blay and Von Mehren, 2011)
Paclitaxel	Microtubule inhibitor, Bcl-2 inhibitor	Inhibits cell cycle progression by inducing mitotic arrest	Neuroprotective, reduction in tau hyper-phosphorylation	PI3K/AKT, MAPK and EGFR pathway	AD	(Li et al., 2003) (Weaver, 2014)
Pazopanib	Tyrosine kinase inhibitor	Inhibits Raf-MAPK/ERK pathway	JAK-STAT, MAPK and PI3K-Akt pathway	Acetylcholinesterase inhibitor, Reduces tau hyper-phosphorylation	AD	(Javidnia et al., 2017) (Zhao et al., 2014)
Rituximab	Monoclonal antibody	Induces CD20 cell death, cytotoxicity, apoptosis and sensitization to chemotherapy	Reduction in B cell population	Complement dependent cytotoxicity	MS	(Weiner, 2010) (Naegelin et al., 2019)
Sunitinib	Tyrosine kinase inhibitor	Stops tumor cell proliferation and angiogenesis	JAK-STAT, MAPK and PI3K-Akt pathway	Acetylcholinesterase inhibitor, an Angiogenesis inhibitor, Inhibits Nitric oxide production	AD	(L. Huang et al., 2016) (Cui et al., 2014)
Saracatinib	Src and Bcr-Abl tyrosine-kinase inhibitor	Anti- invasive and anti-tumor	JAK-STAT, MAPK and PI3K-Akt pathway	Rescues spatial memory deficits and synapse loss	AD, PD	(Kaufman et al., 2015; Nam et al., 2013)
Tamibarotene	Retinoid x Receptor agonist	Inhibits retinoid signaling	Retinoid signaling pathways	Reduction in Aβ, Reduction in proinflammatory cytokines & chemokines.	AD	Fukasawa et al. (2012)
Thalidomide	TNF alpha inhibitor, an Angiogenesis inhibitor	Inhibits angiogenesis and cytokine production. Immunomodulation.	Ubiquitin/Proteasome System	Reduction of Aβ, Microglial activation, Beta secretase 1 (BACE1) enzyme inhibition, Reduction in proinflammatory TNF-α	AD	(Tamilarasan et al., 2006) (He et al., 2013) (Mujagić et al., 2002)

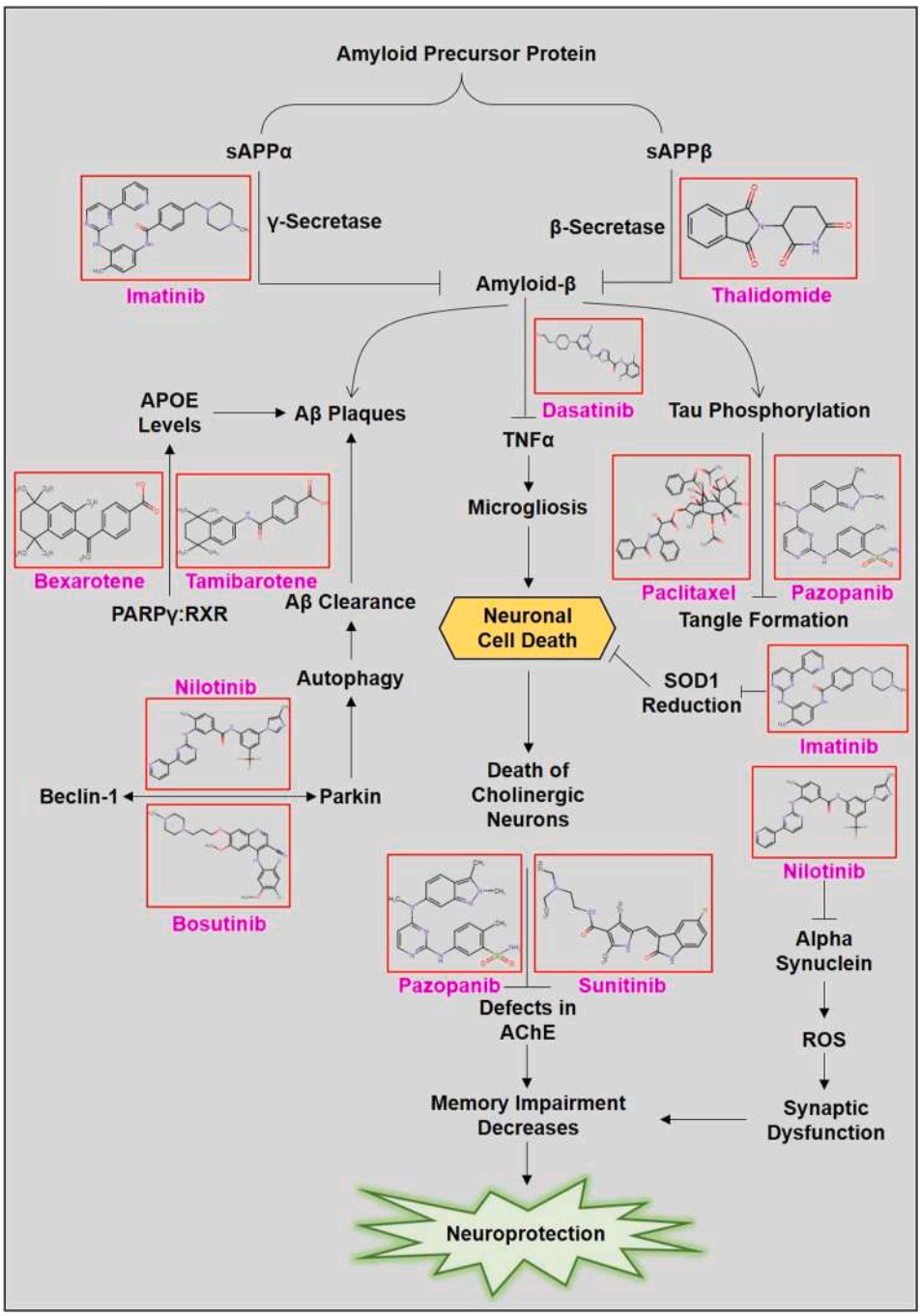

Fig. 3. Schematic representation of the repurposed anticancer kinase inhibitors in neurodegenerative disorders: Pointed arrows represent pathway activation, and blunt arrows represent pathway inhibition. Aβ clearance, inhibition of tau hyper-phosphorylation, and APP processing are the significant events targeted by anticancer drugs in AD. α–syn aggregation and SOD1 mutation are inhibited in the case of PD and ALS, respectively. Thalidomide and Imatinib reduce Aβ level in AD. Bexarotene and Tamibarotene help to increase APOE levels. Nilotinib and Bosutinib enhance the interaction of beclin-1 and parkin and help in amelioration of Aβ peptides. Both Sunitinib and Pazopanib inhibit the activity of Acetylcholinesterase (Ache). Paclitaxel and Pazopanib both reduce tangle synthesis by inhibiting tau hyper-phosphorylation. Dasatinib exerts neuroprotection in AD by inhibiting microgliosis. In PD, Nilotinib reduces α-syn aggregation. In ALS, Imatinib reduces SOD1 mutational changes.

5.2. Parkinson's disease

One of the most accepted hypotheses for the progression of PD is the accumulation of α-synuclein, which increases oxidative stress and eventually leads to dopaminergic neuronal cell death. In an animal model, it was demonstrated that knockdown of c-Abl, which phosphorylates parkin, triggers the mitochondrial apoptotic signaling cascade resulting in mitochondrial dysfunction and cell death via three potent mechanisms. It leads to the suppression of parkin phosphorylation, upregulation of parkin interacting substrates, and inhibiting the activity of aminoacyl-tRNA synthetase complex-interacting multifunctional protein 2 (AIMP-2) (Hantschel and Superti-Furga, 2004; Imam et al., 2011; Ko et al., 2010). Nilotinib, an anti-cancer drug targeting c-Abl, prevents α-synuclein aggregation and neuronal cell death, which improve movement defects in the PD animal model (Karuppagounder et al., 2014). In another study, it was found that under oxidative stress conditions, c-Abl phosphorylates parkin, regulates its cytoprotective function, and inhibits ubiquitin-dependent degradation. A clinical study was conducted to test the potential of Nilotinib on 12 PD patients (Table 4). The results showed good brain permeation and pathological significance with some side effects (Athauda and Foltynie, 2018). An *in silico* study concluded the neuroprotective properties of Dabrafenib for PD and showed its neuroprotective function by inhibition of the phosphorylation of JNK/c-Jun and by activating ERK *in vitro* and *in vivo* (Uenaka et al., 2018).

5.3. Amyotrophic Lateral Sclerosis

ALS is a neurodegenerative disorder characterized by loss of motor neurons, also called Lou Gehrig's or Charcot disease, which decreases

Table 4
List of clinical trials conducted with anticancer drugs for the major five NDDs (Adapted from ClinicalTrials.gov).

S. No.	Study	Clinical Phase	Year of study	Study Design	Status	Results/Effects
1	NCT00140452 (Thalidomide)	Phase II	2005	Thalidomide tablets were given to 40 ALS patients for a 12-week period with an initial dose of 100 mg for six weeks and a progressive increase of 50 mg per week until 400 mg/day dose.	Terminated	More than half of the patients did not enter the trial. Remaining participants were not able to reach the estimated therapeutic dose due to reported adverse events
2	NCT00436826 (Cladribine)	Phase II	2006	Two hundred participants already receiving IFN-beta therapy were given 3.5 mg/kg total dose of cladribine along with placebo and IFN-β (44mcg) thrice a week.	Completed	Decreased relapses, reduced MRI lesion activity with some side effects like lymphopenia
3	NCT01094340 (Thalidomide)	Phase II/ III	2010	Total of 20 participants. Given a fixed dose of Thalidomide for 24 weeks.	unknown	Results unavailable
4	NCT01120002 (Tamibarotene)	Phase II	2010	Total of 50 participants. Given Tamibarotene (2 mg) & placebo capsule every day.	unknown	A trial is still under the experimental approach. Phase III still under consideration.
5	NCT01257581 (Tamoxifen)	Phase II	2010	A randomized, placebo, double-blind clinical trial of 30 participants clinically diagnosed with ALS were given regular doses of Tamoxifene and placebo drug.	Completed	Modest inhibitory effect on ALS progression.
6	NCT01433497 (Masitinib)	Phase III	2011	Total of 656 patients in 2 experimental groups. Group 1 received masitinib (4.5 mg/kg) twice daily, while patients in group 2 received increased dose (6 mg/kg) after three months. Placebo was given the same dose.	Active but not recruiting	The trial is in the non-recruiting phase
7	NCT01864655 (Saracatinib)	Phase I	2013	24 participants divided into three following groups; each was given Saracatinib at doses of 50 mg, 100 mg, 125 mg or placebo daily for 4 weeks.	Completed	Saracatinib was reasonably safe and well-tolerated in mild to moderate AD patients
8	NCT02588677 (Masitinib)	Phase II/ III	2013	Experimental drug masitinib was given to 394 participants along with riluzole at two different doses-masitinib 3 mg/kg/day and masitinib-4.5 mg/kg/day	Completed	Results not available.
9	NCTO1782742 (Bexarotene)	Phase II	2013	Total of 20 participants. Given 75 mg of Bexarotene for one week followed by 150 mg for weeks 2–4. Open-label phase for weeks 5–8 (150 mg drug for four weeks) one placebo capsule for week 1. two tablets for weeks 2–4. An open-label phase of weeks 5–8 (150 mg drug for four weeks)	completed	No amyloid reduction in ApoE4 carriers, the reduction was found in ApoE4 non-carriers. Increased levels of blood lipid levels were found
10	NCT02281474 (Nilotinib)	Phase I	2014	Oral nilotinib was given to patients daily for six months	completed	Results not available.
11	NCT03205488 (Nilotinib)	Phase II	2017	A total of 75 participants were assigned to 3 different groups. Received daily dose of placebo, nilotinib (150 mg), and nilotinib (300 mg) for 12 months period.	Active but not recruiting	Expected to be an effective and safe drug for PD. Early outcomes have shown improvement in motor symptoms
12	NCT02947893 (Nilotinib)	Phase II	2017	Total of 42 participants with mild to moderate AD Twenty-one patients assigned to group 1 treated with the placebo drug one capsule every day for 6 months. Two capsules every day for the subsequent 6 months.	Active but not recruiting	Reduction in β-amyloid plaques and phosphorylated tau tangles. It can penetrate the blood-brain barrier.
13	NCT03193086 (Alemtuzumab)	Phase I	2017	Total of 35 participants. Initial treatment with 60 mg alemtuzumab over a five-day course followed by 36 mg intervention of the drug over a three-day course.	Recruiting	Trial is ongoing
14	NCT03056495 (Vorinostat)	Phase I b	2017	An open label non-randomized, dose-finding trial in patients with mild AD The first part of the study will be escalation study and in the second part dose confirmation will be carried out	Recruiting	Trial is ongoing
15	NCT03674099 (Imatinib)	Phase II	2018	Imatinib (400 mg) will be given twice daily for 14 days along with methylprednisolone	Recruiting	Trial is ongoing
16	NCT03979456 (Rituximab)	Phase III	2018	200 participants receiving rituximab(500 mg) for four years	Recruiting	Trial is ongoing
17	NCT03888222 (Bosutinib)	Phase II	2019	A total of 30 participants was divided into three groups (n = 10). Each group was treated with Bosutinib/placebo with two doses of 100 mg and 200 mg. Further randomization into groups each with n = 15	Recruiting	Trial is ongoing
18	NCT03661125 (Saracatinib)	Phase I	2019	30 participants are divided into two groups. In first arm of study one group would be given 100 mg Saracatinib for 2 weeks while others would be given a placebo. In the second arm, groups would cross over, that is, the group that was given a drug in first arm would be given placebo and other would be given 100 mg drug for 2 weeks.	Recruiting	Trial is well tolerated at Phase I and further moved towards Phase II. Final outcome still under experimentations
19	NCT04070378 (Daratumumab)	Phase II	2019	An open label study in patients with AD. Patients will be infused with Daratumumab SC 1800 mg once weekly for 8 weeks followed by the same dose of drug every 2 weeks for 16 weeks.	Recruiting	Trial is ongoing
20	NCT04326283 (Trametinib)	Phase I/ II	2020	A randomized, multi-center, active-controlled clinical trial. Patients with ALS will be given three different doses (0.5 mg, 1 mg, 2 mg) of drugs Tamoxifen and Riluzole (Active comparator)	Recruiting	Trial is ongoing
21	NCT04063124 (Dasatinib + Quercetin)	Phase I/ II	2020	Total 40 participants were given combination treatment of D& Q for 2 days on/14 days off for 12 weeks.	Recruiting	Trial is ongoing

muscle movement and size. Being an untreated disorder, drug discovery through drug repositioning has been of utmost importance, especially for anticancer drugs because of similarity up to some extent in disease progression. A research was conducted to validate the potency of Imatinib and related inhibitors (Dasatinib and Bosutinib) in ALS mouse models. Imatinib showed good results with a significant reduction of soluble SOD1. A study on the mouse antimetabolite anticancer drug 5-fluorouracil (5-FU) in mice models of ALS suggests that the drug improves motor performance; still, the mechanism of action was not precise (Rando et al., 2019). Scientists from Ben Gurion University mark a statement that Rituximab, an anticancer drug restores the primary immune cells of the brain and helps to extend the life expectancy of ALS patients. Another chemotherapeutic agent Masitinib is a potent regulator of mast cell and microglial cell activity. The clinical results have shown the neuroprotective role of Masitinib in ALS. A compelling report was published in the 2019 Muscular Dystrophy Association Conference that Masitinib is capable of regulating the action of macrophages, neutrophils, mast cells, and Schwann cells-all the four responsible for neurogenic inflammation (J.S. and O., 2017; Khairoalsindi and Abuzinadah, 2018). A phase II clinical trial was initiated to determine the anti-neuroinflammatory properties of Thalidomide in ALS patients. The drug may have a possible role as a neuroinflammation inhibition agent (Stommel et al., 2009).

5.4. Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune neurodegenerative disorder that remains untreated. Drug repurposing using anticancer found to be a promising therapeutic strategy against multiple sclerosis. Till date, six anticancer drugs, viz. Mitoxantrone, Alemtuzumab, Cyclophosphamide, Cladribine, Rituximab, and Methotrexate are investigated for MS. Alemtuzumab, a monoclonal antibody targeted against CD-52 has excellent promise for MS (Coles, 2013a, 2013b; Coles et al., 2012; Jones et al., 2010). A recent review reported the efficacy of Alemtuzumab as a disease-modifying drug for MS highlighting its biological and clinical importance (Gallo et al., 2017). The phase II/III clinical trials supported the safety profile of the drug for MS treatment with mild to moderate infection problems (Havrdova et al., 2015). Another monoclonal antibody (mAb) Rituximab helps to reduce the relapse rate and disease advancement in MS (Salzer et al., 2016). A further study confirms that Rituximab depletes B cell populations in MS patients (Naegelin et al., 2019). Mitoxantrone, a chemotherapeutic agent, got approval for its use in MS and in a clinical trial using Mitoxantrone (MX) on MS patients concluded that MX was able to reduce the risk of disease progression up to some extent without any sign of melanoma or other types of tumors with minimal side effects of drug dosage. The study gained evidence after ten years of treatment, which concluded that MX is a safe and effective treatment against the patient with relapsing-remitting MS (RRMS) (Chartier et al., 2018; Hartung et al., 2002). Cyclophosphamide (CYC), an anti-replicative anti-mitotic agent also showed anti-inflammatory action by increasing the production of inflammatory cytokines and increasing the secretion of anti-inflammatory cytokines (Smith et al., 1997). CYC can cross the blood-brain-barrier and has good bioavailability in the brain and help to stop MS progression (Awad and Stue, 2009; La Mantia et al., 2007; Makhani et al., 2009). Cladribine and Methotrexate also advocate their potential benefit in different studies, but the exact mechanism of their action in MS is not precise yet (Ashtari and Savoj, 2011; Cook et al., 2011; Giovannoni et al., 2010; Gray et al., 2003; Jacobs et al., 2018). A study suggested the role of Imatinib in MS treatment also. Treatment of experimental autoimmune encephalomyelitis (EAE), an MS animal model, with Imatinib showed notable inhibition in disease progression (Azizi et al., 2014).

5.5. Huntington's disease

A little information is available regarding the significance of anticancer drugs in HD pathophysiology. A phase 1 clinical trial is recruiting at the Georgetown University Medical Center (GUMC) to check the safety and efficacy of Nilotinib in HD patients (Table 4). The work is based on the fact that Nilotinib clearing the protein aggregation in PD and Dementia with Lewy bodies and may also reduce huntingtin protein accumulation.

6. How anticancer drugs are neuroprotective?

The principal idea behind drug repurposing is that a single protein/enzyme/gene may have a crucial role in the pathogenesis of more than one disease. Most targeted drugs are not uniquely specific, but instead exhibit a broad range of target selectivity. Utilizing such "off-target activity" can lead to novel therapeutic approaches (Palve et al., 2020). The common link between signaling mechanisms and genes involved in regulating diverse cellular functions advocate the repurposing significance of oncology drugs in neurodegeneration. However, the exact mechanisms and protein targets are not specified for all the repurposed drugs. Still, some anticancer drugs share common targets and common biological mechanisms in NDDs, as well as. The most frequent targets shared between cancer, and NDDs are the tyrosine kinases. Src family kinases, the non-receptor tyrosine kinases, are the mediators of tumor development, tumor metastasis, and angiogenesis (Zhang and Yu, 2012). Src family members, Fyn and Lck, are involved in tau phosphorylation (Scales et al., 2011). c-Src kinase has a neuroprotective role against glutamate-induced neurotoxicity (Khanna et al., 2007). Another non-receptor tyrosine kinase Abl is found to be overexpressed in many cancers and is associated with tumor proliferation, growth, and metastasis (Wang and Pendergast, 2015). Abl activation is also coupled with many neurological conditions under oxidative stress and DNA alterations (Schlatterer et al., 2011). Additional shared target genes in cancer and NDDs are VEGF and Platelet-derived growth factor (PDGF). Both VEGF and PDGF are the key regulators of angiogenesis, promoting tumor growth and metastasis (Carmeliet, 2005). VEGF and PDGF have remarkable roles in neurogenesis and neuroprotection. Hypoxic conditions stimulate VEGF production that exerts protective effects on neurons, glial cells, astrocytes, and Schwann cells (Namiecińska et al., 2005). VEGF-B is a protective factor in PD and ALS, where it improves mitochondrial metabolism (Caballero et al., 2017). PDGF has neuroprotective effects against oxidative stress and glutamate-N-methyl–D-aspartate (NMDA) receptor-induced neurotoxicity by activation of PI3K/Akt and MAPK pathways (Funa and Sasahara, 2014). Another essential common target gene for anticancer drugs in cancer and NDD is RAR.

RARs are the transcription factors involved in cell growth and differentiation (Altucci et al., 2007). The RAR agonists reduce neuroinflammation and neurodegeneration by inhibiting different cytokines, chemokines, and by inhibiting the accumulation of Aβ oligomers (Das et al., 2019). An important cytokine TNF-α plays a pathological role in both cancer and NDDS. TNF-α is a potent pleiotropic cytokine with antitumor activities. It promotes cancer progression by inducing nuclear factor kappa light chain-enhancer of activated B cells (NF-κB) mediated inflammation (Balkwill, 2006; Josephs et al., 2018). TNFα is the primary key factor involved in neuroinflammation associated with the major neurodegenerative diseases (Frankola et al., 2011). It is a potent enhancer of γ-secretase enzyme activity and promotes microglial activity in CNS and potentiates excito-neurotoxicity (Olmos and Lladó, 2014).

7. Protective role of anticancer drugs against neurotoxins

Neurotoxins such as glutamate, domoic acid, amyloid-β, α-synuclein, β-N-Methylamino-L-alanine, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine,1-methyl-4-phenylpyridinium, rotenone, 3-Nitropropionic acid, NO and free radicals induce neuronal injury and neuronal toxicity through different mechanisms such as mitochondrial

dysfunction, apoptosis, autophagy clearance, and oxidative stress. However, a few anticancer drugs are identified till the date, which overcomes the adverse effects of these neurotoxins and helps in neuroprotection, as depicted in Fig. 4. NO is a neurotransmitter, which is vital for normal brain functioning. Still, excessive production of NO is associated with the pathogenesis of AD, PD, and MS (Stewart et al., 2002). In AD brains, Aβ stimulates NO production, which leads to mitochondrial dysfunction and causes neurotoxicity (De La Torre and Stefano, 2000). Prolonged exposure of SH-SY5Y cells to NO generates tau neuro-pathogenesis by induction of tau oligomers formation (Takahashi et al., 2012). NO is responsible for neuronal death of dopaminergic and motor neuron loss associated with PD and ALS, respectively (Steinert et al., 2010). A study gives evidence for an increase in Reactive nitrogen species (RNS) in the CSF of MS patients' brains (Encinas et al., 2005). A work by Chinese researchers confirmed that Sunitinib blocks NO overproduction by inhibiting neuronal Nitric oxide synthase (nNOS) (Cui et al., 2014) The neurotoxic effects of oxidative stress in neurological conditions are confirmed by many studies. Oxidative stress created by reactive oxygen species (ROS) releases free radicals that contribute to disease pathogenesis by affecting different cellular functions. The major adverse effects are mitochondrial dysfunction and inhibition of the electron transport chain (Federico et al., 2012; Niedzielska et al., 2016; Subramaniam and Chesselet, 2013). Aβ and α-synuclein are the significant neurotoxins associated with AD and PD pathology. The intracellular Aβ oligomers exert their toxic effects by proteasome dysfunction, tau hyper-phosphorylation, lipid peroxidation, altered tau aggregation, and endothelial cell damage (Lublin and Gandy, 2010; Rauk, 2008).

Similarly, α-syn, in PD brains, is responsible for autophagy inhibition, mitochondrial dysfunction, inhibition of the proteasome, oxidative stress, and neuroinflammation (Wong and Krainc, 2017). Anticancer drugs Bexarotene, Thalidomide, Tamibarotene, and Nilotinib can reduce toxic levels of Aβ, while Nilotinib also clears α-syn from the brain. Another factor contributing to neuronal toxicity is the microglial cell. Microglia is the professional phagocytic cells of the CNS but depending on the environmental conditions exerts neurotoxic effects. Microglia releases several ROS as NO, peroxynitrite, hydrogen peroxide, and superoxide that lead to oxidative damage. These cells also cause excito-neurotoxicity by secreting glutamate (Takeuchi, 2010). Dactolisib, an anticancer tyrosine kinase inhibitor reduces microglial activation and Aβ plaques in AD mice (Bellozi et al., 2016).

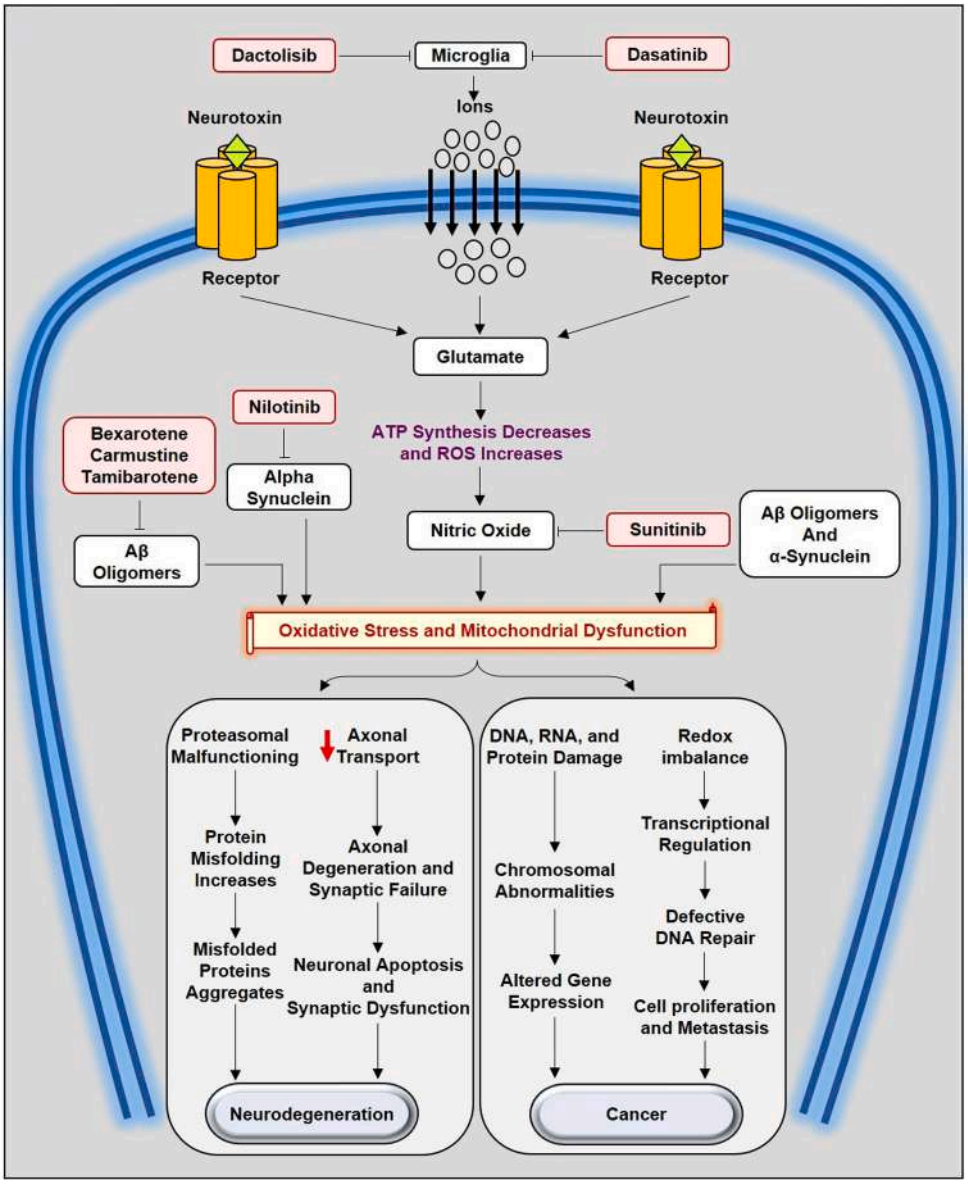

Fig. 4. Role of anticancer drugs against various neurotoxins: Effect of neurotoxins such as amyloid-beta, glutamate, α-synuclein, nitric oxide and microglia in the progression of neurodegenerative diseases. The microglial cells induce glutamate toxicity which in turn causes reduced ATP synthesis and ROS mediated oxidative stress. The Reactive nitrogen species induce the nitric oxide release, which is a potent neurotoxin. The major NDDs are marked by abnormal protein aggregation, that in turn causes neurotoxicity and neuronal death. The combined effect of oxidative stress and mitochondrial dysfunction promotes synaptic dysfunction and neurodegeneration. The adverse consequences of oxidative stress and mitochondrial dysfunction also affect the different cellular phenomenon in cancer such as DNA, RNA and Protein damage, abnormal cell proliferation, metastasis, chromosomal abnormalities and redox imbalance. Anticancer drugs (Highlighted in pink) reverse the effects of various neurotoxins and thus ameliorate neurotoxicity.

8. Kinase inhibitor therapeutics for cancer and neurodegenerative disorders

Protein kinases are a distinct class of enzymes that play an integral role in different cellular processes, and their dysregulation is associated with various pathological conditions. The role of kinase inhibitors in cancer is well established, where they regulate the activity of kinases involved in uncontrolled cell division, proliferation, and invasion (Madhusudan and Ganesan, 2004) (Lakkakula et al., 2019). Thus far, most of the kinase inhibitors are approved for oncology indications; however, some of them have recently gained attention in Rheumatoid arthritis, inflammatory disorders, and several chronic neurodegenerative disorders. It has been suggested that protein kinases play an essential role in the significant domains related to AD, such as tau phosphorylation, APP processing, neuroinflammation, and neurotoxicity. For instance, GSK3 and CDK5 have been studied concerning tau phosphorylation and APP processing (Savage and Gingrich, 2009). GSK3 inhibitors have been reported to be useful in ALS as well, where they delayed the onset of disease. Similarly, the role of CDK5 has also been confirmed in PD and HD, where it is the mediator of dopamine and glutamate neurotoxicity (Smith et al., 2003) (Paoletti et al., 2008).

p38 Mitogen-activated protein kinase (p38 MAPK) is another kinase of interest in neuroinflammation where it regulates the synthesis of inflammatory cytokines such as TNF-α. Activation of p38 MAPK has also been reported in astrocytes and neurons during cerebral ischemia (Irving et al., 2000). Significant studies have demonstrated the role of Abelson non-receptor tyrosine kinases (Abl) kinases in neurodegenerative disorders (Alvarez et al., 2004), as illustrated in Fig. 5. Several studies have shown that mutation in c-Abl leads to defective neurogenesis and different deleterious neurological phenotypes (Schlatterer et al., 2011). Abl was found to be upregulated in the brain region and causes loss of neuronal cells, impaired motor activity, cognitive

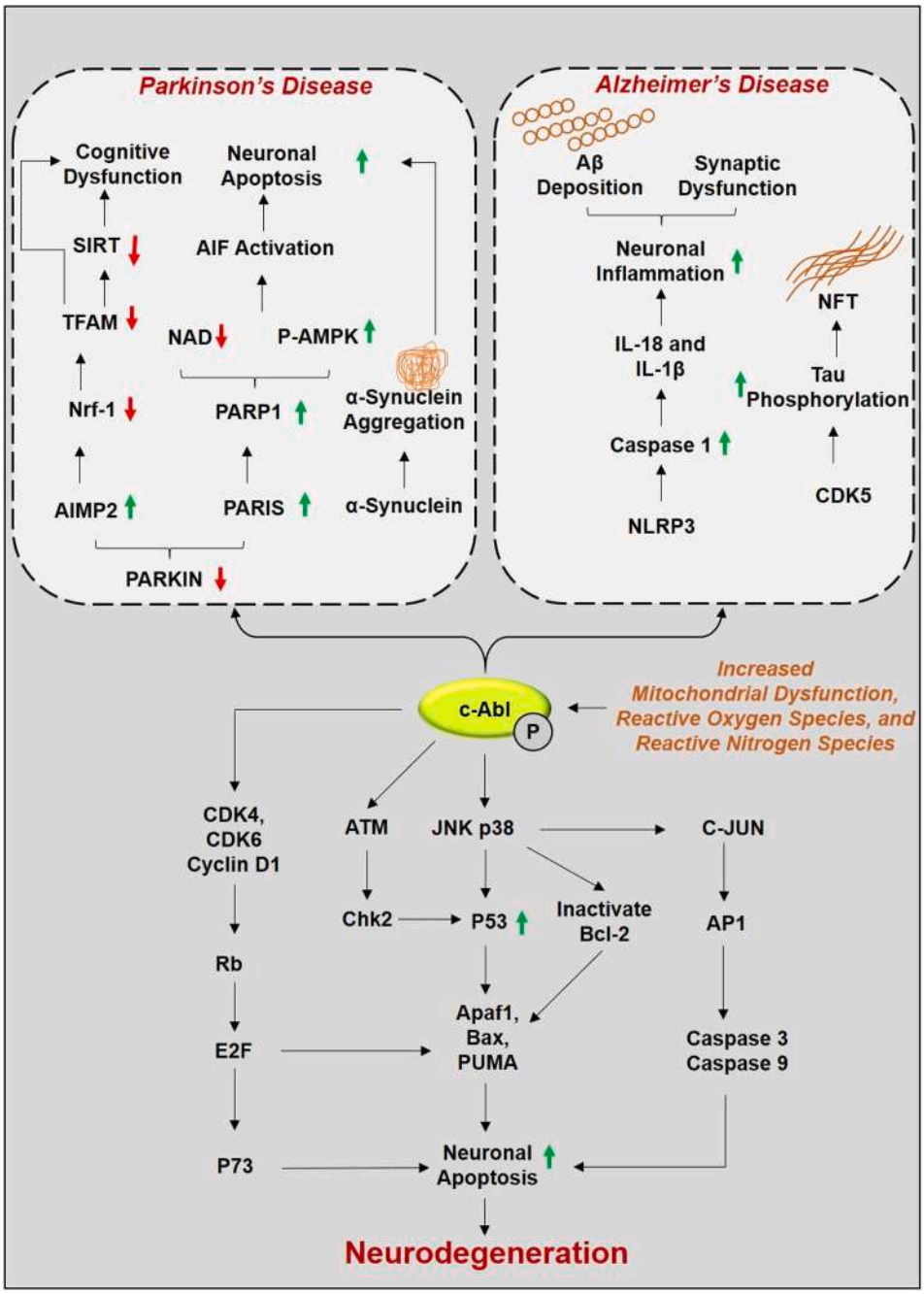

Fig. 5. The potential role of c-Abl in neurodegenerative disorders: Aging, neurotoxins, oxidative stress, and mitochondrial dysfunction promotes the activation of non-receptor tyrosine kinase c-Abl. In PD, activated c-Abl causes parkin inactivation, accumulation of parkin substrates Poly ADP ribose (PARIS), and Aminoacyl tRNA synthetase complex-interacting multifunctional protein 2 (AIMP2) and alpha-synuclein aggregation. In AD, the major role of c-Abl is tau phosphorylation by increasing cyclin-dependent kinase 5 (CDK5) concentration. The phosphorylated CDK5 then induces tau phosphorylation and tangle formation. C-Abl also promotes the activity of intracellular inflammasome complex NLRP3 that upregulates the synthesis of various cytokines and thus induce neuroinflammation. c-Abl regulates the expression of p53 by inducing the activities of Cyclin-dependent kinases 4 & 6 (CDK 4 & 6), cyclin D1, ATM (Ataxia Telangiectasia), Rb (Retinoblastoma) genes and their downstream molecules. The overexpressed p53, a tumor suppressor, further promotes caspase-dependent neuronal apoptosis.

dysfunction, and learning deficits which could be reversed by the potential action of c-Abl inhibitors. c-Abl inhibitors inhibit the phosphorylation of CDK5, regulate the phosphorylation of alpha-synuclein, Parkin, and associated substrates such as the NLR family pyrin domain containing 3 (NLRP3), Parkin interacting substrate (PARIS), AIMP2, Poly (ADP ribose) (PARP) and JNK/p38. (Brahmachari et al., 2016; Hebron et al., 2013; Tanabe et al., 2014; Wu et al., 2016). Similarly, ERK is thought to be involved in the regulation of neuronal apoptosis. Studies have shown the presence of activated ERKs in the initial stages of neurofibrillary tangle formation in AD brains. JNK3, a member of the MAPK pathway, is highly expressed in the brain. A study with jnk3 mutant mice has shown protection against 6-hydroxydopamine and MPTP in the dopaminergic neurons in the substantia nigra (Hunot et al., 2004).

Repurposing of kinase inhibitors for the treatment of NDDs is an area of interest for the research community. Several kinase inhibitors have shown success in experimental and clinical studies and have demonstrated their protective effect against signaling mechanisms associated with NDDs. Angiogenesis, PI3/Akt pathway, MAPK pathway, inflammatory responses are the major pathways targeted by kinase inhibitors in both Cancer and neurodegenerative disorders, suggesting their potential repurposing roles. The proposed mechanisms of various kinase inhibitors in neuroprotective pathways are highlighted in Fig. 6.

9. Challenges associated with repurposed anticancer agents

The potential of chemotherapeutics agents in the repurposing for NDDs has already been shown in the above sections, but drug resistance and toxicity are the major hurdles. Drug resistance is a significant issue in drug development for brain disorders. The two main problems associated with drug resistance in the brain are-the presence of physical barriers such as BBB and CSF barrier, and another is the presence of drug

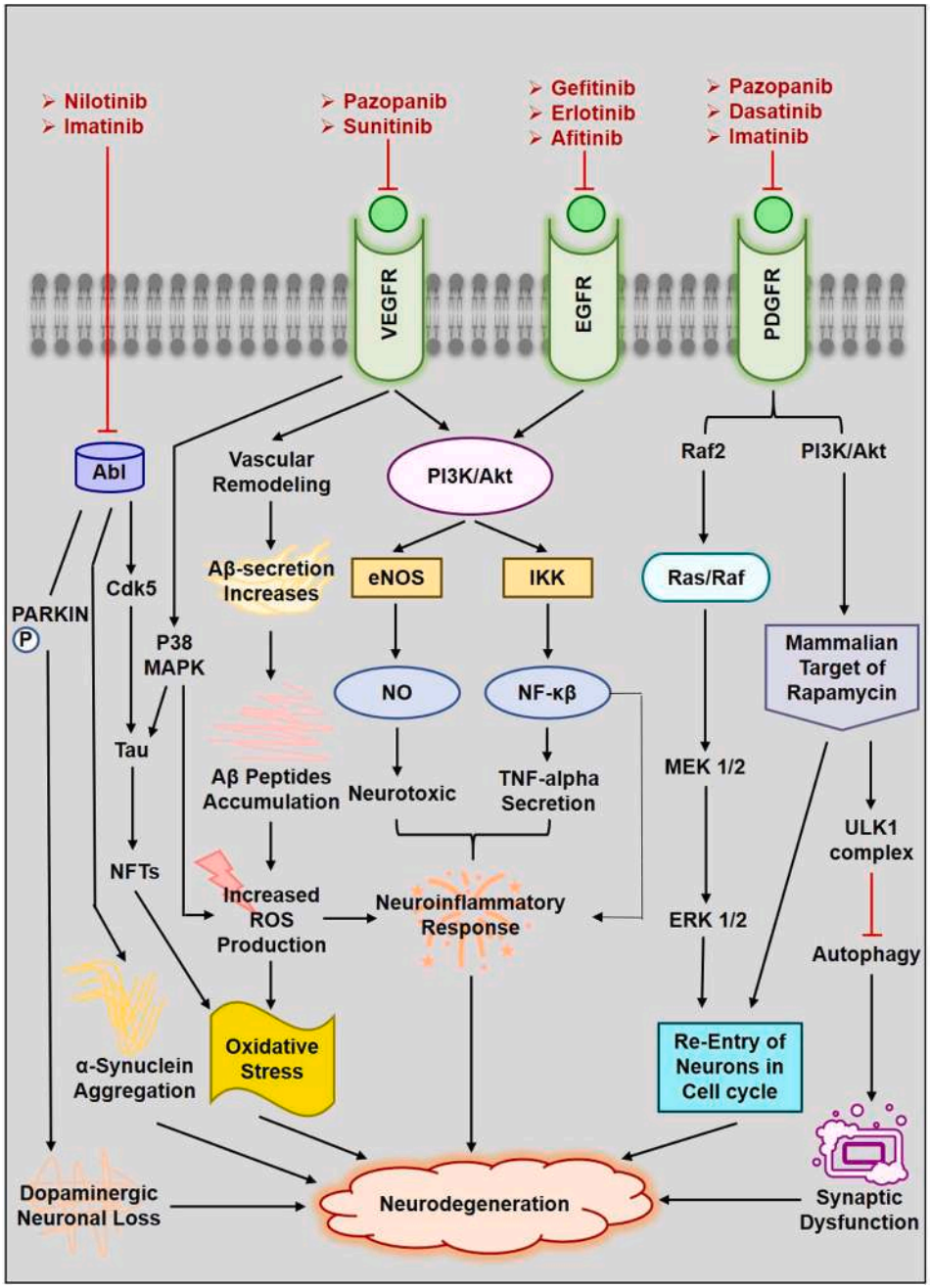

Fig. 6. Proposed mechanism of kinase inhibitors in neuroprotection: Pharmacological inhibition of c-Abl with anticancer drug Nilotinib and Imatinib help to prevent neurofibrillary tangle formation by inhibition of CDK-5 activity. The drugs inhibit PARKIN phosphorylation and compensate for the dopaminergic neuronal loss. Inhibition of Vascular endothelial growth factor receptor (VEGFR) by Pazopanib and Sunitinib may ameliorate Nitric Oxide (NO) toxicity, prevent the release of inflammatory cytokines by the inhibition of p38 kinase, and reduction in ROS production. Gefitinib, Erlotinib, and Afatinib are the Epidermal growth factor receptors (EGFR) that can reduce neuroinflammatory response by inhibition of Tumor necrosis factor-alpha (TNF-α) and also reduce amyloidogenesis. The inhibition of Platelet-derived growth factor receptor (PDGFR) by Pazopanib, Dasatinib, and Imatinib has neuroprotective roles in phosphoinositide-3-kinase/Aky (PI3/A-kt) pathway inhibition that leads to mTOR mediated activation of autophagy and also stop post-mitotic neurons from re-entering in the cell cycle. All the events trigger neuroinflammation and neuronal cell death associated with neurodegeneration.

efflux transporters. P glycoprotein (Pgp) and Multidrug-resistant proteins (MRP) are the two transporters which limit the availability of any drug to the brain (Löscher and Potschka, 2005a, 2005b; Phillips, 2018; Urquhart and Kim, 2009). A study confirms the poor brain penetration of Imatinib due to the overexpression of Pgp. Other chemotherapeutics like paclitaxel, methotrexate, mitoxantrone, and 5-FU also have a restricted approach to the brain (Jacus et al., 2016; Takayama et al., 2002).

Another aspect of being considered is the toxicity associated with anticancer agents. Several anticancer drugs are found to be related to neuronal damage (Ferrier et al., 2013). The major neurological complications related to anticancer drugs are summarized in Table 5. Platinum-based drugs, vinca alkaloids, taxanes, epothilones, proteasome inhibitors, and immunomodulatory drugs are the primary six classes of antineoplastic, resulting in chemotherapy-induced peripheral neuropathy (CIPN) (Starobova and Vetter, 2017). Thalidomide, an anticancer drug gain attraction due to its neuroprotective role in AD. Depending upon the dose, it causes peripheral neuropathy in 25–75% of patients (Morawska et al., 2015). The antiangiogenic effect of Thalidomide causes neuronal hypoxia and secondary ischemia, accompanied by irreversible neuronal damage (Jongen et al., 2015; Tamilarasan et al., 2006). One of the most devastating side effects of Thalidomide is its teratogenic effect as the drug targets tissue-specific vessels, causing their loss through oxidative stress induction and causes severe embryopathy (Vargesson, 2015). A study by Isidori et al. also highlighted the teratogenic effects of anticancer drugs Fluorouracil and Imatinib in frog embryos where the drugs have shown adverse effects on embryogenesis and induced developmental malformations (Isidori et al., 2016). Paclitaxel, another promising antitumor agent, triggers neuroinflammation by inducing the production of pro-inflammatory cytokines (Zaks-Zilberman et al., 2001). A single high dose of paclitaxel results in sensory neuropathy 24–72 h after dose intake in 59–78% of patients (Rowinsky et al., 1993). Tyrosine kinase inhibitors, the most attractive class of prospective neuroprotectants, are also associated with neuropathy. Peripheral neuropathy has been reported with Imatinib (Chakupurakal et al., 2011). A case study highlighted the link between Dasatinib and demyelinating peripheral neuropathy, possibly by immune-mediated problems (Ishida et al., 2018).

Apart from neurological toxicities and neuropathies, several other long terms- and short-term side effects were reported for chemotherapeutic drugs. A review by Rapoport et al. highlighted that chemotherapy-induced nausea, and vomiting (CINV) is a frequently appeared and poorly controlled symptom associated with chemotherapy (Rapoport, 2017). Nephrotoxicity, including hepatic dysfunction, obstructive jaundice, metabolic disturbances, glomerular injury with proteinuria, and acute kidney injury, is another complication associated with anticancer agents (Perazella and Moeckel, 2010). Many anticancer drugs such as Methotrexate Imatinib, Dasatinib, Thalidomide, and nitrosoureas are found to be associated with pulmonary toxicities such as pulmonary embolism, pneumonitis, pleural effusions and pulmonary hypertension (Sharma et al., 2013). Drug-induced liver injury (DILI) is another challenging side effect of chemotherapy. Hepatic failure, steatosis, cirrhosis/fibrosis, disturbed drug metabolism is the identified symptoms accompanied with chemotherapy treatment. All the mentioned side effects and the associated clinical manifestations pose a challenge to repurpose anticancer drugs. Altogether, close monitoring of the drug mechanisms of action, evaluation of side effects, identifications of effective drug doses are the prerequisite steps in the repurposing of chemotherapeutic drugs.

Table 5
Summary of the major neurological complications associated with the repurposed anticancer drugs.

Anticancer drugs	Neurological symptoms	References
Carmustine, Cisplatin, Methotrexate, Vincristine	Cranial neuropathy	Stone and DeAngelis (2016)
Paclitaxel, Docetaxel, Vincristine, Vinblastine, Cisplatin, Carboplatin	Peripheral neuropathy	(Park et al., 2013) (Kim and Johnson, 2017) (Cavaletti and Marmiroli, 2010)
Cisplatin, Imatinib	Myalgia (muscle symptoms)	Soffietti et al. (2014)
Oxaliplatin, 5-Fluorouracil, Vincristine	Cerebellar dysfunction	(Kuebler et al., 2007) (Stone and DeAngelis, 2016)
Cisplatin, Cyclophosphamide, 5-Fluorouracil, Vincristine, Methotrexate, Sorafenib, Sunitinib	Encephalopathy	Sioka and Kyritsis (2009)
Methotrexate, Cyclosporine	Cerebrovascular diseases	Haykin et al. (2006)
Cyclophosphamide, Methotrexate	Seizures	Giglio and Gilbert (2010)
Imatinib	Cerebral haemorrhage	Plotkin and Wen (2003)
Vincristine	Parkinsonism	(Gomber et al., 2010) (Madsen et al., 2019)
Carmustine, Vincristine, Vinblastine, Fluorouracil	Ocular toxicity/ neuropathy	(Cruciani et al., 1994) (Fraunfelder and Meyer, 1983)
Fluorouracil, Methotrexate, Carmustine	Leukoencephalopathy	Yang and Moon (2013)
Methotrexate	Myelopathy	Murata et al. (2015)
Thalidomide	Epilepsy	Stephenson (1976)
Methotrexate	Stroke/Acute focal encephalopathy	Dropcho (2011)

10. Future perspectives and conclusions

Neurodegeneration and cancer share an exclusive association of genes and proteins involved in different signaling pathways. This review focuses on the shared genes and signaling pathways between the two most threatening diseases. The shared mechanisms of various signaling pathways support the intriguing link between cancer, AD, PD, HD, ALS, and MS. Drug repositioning presents an electrifying opportunity for new drug development for NDDs. Currently, anticancer drugs are attaining more attractions for drug repurposing for NDDs. Based on the available literature, we found that anticancer drugs offer neuroprotective function in different aspects as clearing toxic protein aggregation, resisting neuroinflammation, and immunomodulation. The major drug classes exhibiting promising repurposing results are-kinase inhibitors, antimetabolites, alkylating agents, and antibodies where kinase inhibitors are gaining most of the interest to date. Protein kinases have been identified to play a central role in several pathologies related to NDDs. The cellular and animal model studies have demonstrated the success of these small-molecule drugs for NDDs and have encouraged their repurposing potential. However, the exact mechanistic role of these drugs in CNS diseases is still unknown and demands further investigations.

Furthermore, the neurotoxic effect of certain anticancer drugs should be taken into consideration as it is the biggest challenge in drug repurposing process. Some of the drugs described in this review are already in clinical trials for repurposing treatment, but further *in vitro* and *in vivo* experiments are in dire need to identify the exact mechanism of action, off-target interactions, and side effects for their repurposing. The dual nature of some anticancer drugs is also a matter of future research to identify the neurotoxic or neuroprotective functions associated with them.

In conclusion, the repurposing of chemotherapeutic drugs for NDDs opens new possibilities in context with the urgent necessity of drug development for these disorders. The pairing of computational and experimental techniques with efficient clinical trials will uncover the safety, tolerability, and therapeutic effect of anticancer drugs for NDDs in the immediate future.

Author agreement

All authors have seen and approved the final version of the manuscript for submission. This article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Author's contribution

P.K. conceived and designed the manuscript. D.A. has collected, analyzed, and critically evaluated these data. R.G. has helped in the artwork and formatting. R.T. has contributed to the signaling mechanism and data analysis. S.S. has contributed in art work and brain tumor portion R. K. A. helped in data analysis, and provided critical feedback. P.K and D.A. analyzed the entire data and wrote the manuscript.

Declaration of competing interest

All authors have read the manuscript and declared no conflict or competing interests.

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Glossary

5-FU: 5-Flurouracil
ABCA1: ATP binding cassette transporter
ABCG1: ATP binding cassette sub family G
AchE: Acetylcholinesterase
AD: Alzheimer's disease
ADCC: Antibody dependent cell mediated cell cytotoxicity
AIMP2: Aminoacyl tRNA synthetase complex interacting multifunctional protein 2
ALS: Amyotrophic Lateral Sclerosis
Am80: Tamibarotene
APL: Acute Promyelocytic member 1
APOE: Apolipoprotein E
APP: Amyloid precursor protein
ATM: Ataxia telangiectasia mutated
ATP: Adenosine triphosphate
Aβ: Amyloid beta
BACE1: Beta secretase enzyme
BBB: Blood brain barrier
Bcl-2: B-cell lymphoma 2
bFGF: Basic fibroblast growth factor
c-Abl: Abelson tyrosine kinase
CAS: Cationic anionic site
CDK5: Cyclin dependent kinase 5
CNS: Central nervous system
CSF: Cerebrospinal fluid
Cu: Copper
CYC: Cyclophosphamide
DHFR: Dihydrofolate reductase
EAE: Experimental autoimmune Encephalomyelitis
ERK: Extracellular signal regulated kinase
FDA: Food and drug administration
Fe: Iron
GSH: Glutathione
GSH/GSSG/: Reduced/oxidized glutathione
GSK3β: Glycogen synthase kinase 3 beta
GUMC: Georgetown university medical center
HAC: Hydrogen atom count
HBA: Hydrogen bond acceptor
HBD: Hydrogen bond donor
HD: Huntington disease
Htt: Huntingtin
JNK/c-Jun: c-Jun N terminal kinase
KNHIS: Korean national health insurance services
LXR: Liver X receptor
mAb: Monoclonal antibody
MAPK: Mitogen activated protein kinase
MAPK2K: MAPK kinase
MAPK3K: MAPK kinase kinase
MDM2: Mouse double minute 2 homolog
MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRP: Multi drug resistant protein
MS: Multiple sclerosis
MTOR: Mammalian target of rapamycin
MW: Molecular weight
MX: Mitoxantrone
NDDs: Neurodegenerative diseases
NFT: Neurofibrillary tangle
NIH: National institute of health
NLRP3: NLR family pyrin domain containing 3
NO: Nitric oxide
NF-κB: Nuclear kappa light chain-enhancer of activated B cells
NMDAR: N-methyl-D-aspartate receptor
PD: Parkinson's disease
PDGF: Platelet derived growth factor
Pgp: P glycoprotein
PI3K-PKB/Akt: Phosphoinositide-3-kinase-protein kinase B/Akt
PINK1: PTEN-induced kinase 1
PO4: Phosphate
Poly Q: Polyglutamine
PPARγ-RXR: Peroxisome proliferator activated receptor-Retinoid X receptor
PPMS: Primary progressive multiple sclerosis
PS: Presenilin
PSA: Polar surface area
PTEN: Phosphatase and tesin homolog
Rab3A: Ras related protein

RB: Rotatable bonds
RNS: Reactive nitrogen species
RRMS: Relapsing remitting multiple sclerosis
RT PCR: Reverse transcriptase PCR
RTK: Receptor tyrosine kinase
SEER: Surviellance, epidemiology and end results
SOD1: Super oxide dismutase 1
SPMS: Secondary progressive multiple sclerosis
TGFβ: Transforming growth factor beta
TNFα: Tumor necrosis factor alpha
UPR: Unfolded protein response
VEGF: Vascular endothelial growth factor
VEGFR: Vascular endothelial growth factor receptor
Wnt: Wingless type murine mammary tumor virus integration site
Zn: Zinc