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Review article

Exploring the new horizons of drug repurposing: A vital tool for turning hard work into smart work

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ABSTRACT

Drug discovery and development are long and financially taxing processes. On an average it takes 12–15 years and costs 1.2 billion USD for successful drug discovery and approval for clinical use. Many lead molecules are not developed further and their potential is not tapped to the fullest due to lack of resources or time constraints. In order for a drug to be approved by FDA for clinical use, it must have excellent therapeutic potential in the desired area of target with minimal toxicities as supported by both pre-clinical and clinical studies. The targeted clinical evaluations fail to explore other potential therapeutic applications of the candidate drug. Drug repurposing or repositioning is a fast and relatively cheap alternative to the lengthy and expensive de novo drug discovery and development. Drug repositioning utilizes the already available clinical trials data for toxicity and adverse effects, at the same time explores the drug's therapeutic potential for a different disease. This review addresses recent developments and future scope of drug repositioning strategy.

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Contents

1. Introduction . . . 2
2. History of drug repurposing . . . 2
3. Approaches to drug repurposing . . . 2
   3.1. In silico drug repurposing . . . 2
      3.1.1. Text mining approach . . . 3
      3.1.2. Cluster approaches . . . 3
      3.1.3. Propagation approach . . . 5
      3.1.4. Semantics approach . . . 5
      3.1.5. Databases and resources . . . 5
   3.2. Biological approaches . . . 7
   3.3. Experimental approaches . . . 7
   3.4. Mixed approaches . . . 7

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3.5. Knowledge-based repurposing . . . 7
4. Drug repurposing in various diseases . . . 7
4.1. Drug repurposing for CNS disorders . . . 7
4.2. Drug repurposing for cancer . . . 8
4.3. Drug repurposing for infectious diseases . . . 9
4.4. Drug repurposing in other diseases . . . 12
5. Conclusion and future perspectives . . . 12
References . . . 13

1. Introduction

The discovery process of a potential new drug is time-consuming [1]. The development and approval of active pharmaceutical ingredient can take 10–15 years. Pharmaceutical companies spend nearly 1.2 billion U.S. dollars for bringing the new drug to the market. Researchers identify particular cellular and genetic factors that play a major role in each disease condition [2]. They target these biological markers with newly developed biological and chemical agents. Sometimes the developed molecules show drug-like effects. During the discovery process, nearly 5000 new compounds are identified and undergo various preclinical evaluations [3]. Out of these compounds, on an average approximately 5 are selected for further clinical development. After several years of clinical evaluations only one of these compounds would finally receive approval for human use [4]. Fig. 1 shows the steps involved in the drug development and drug repositioning. The discovery and developmental stages of new drug molecules include target identification (targeting cellular and genetic markers associated with a particular disease), target prioritization/validation (identification of developed molecule that have an effect on selected target), lead identification (molecules capable of treating the disease), and lead optimization (comparison of properties of various lead compounds and selection of lead compound with the greatest potential) [5,6]. Preclinical studies which follow drug discovery ensure the safety of the drug by laboratory and animal testing. After the preclinical research, investigational new drug (IND) application is submitted to FDA for permission to conduct clinical testing [7]. Clinical research phase includes phase I, II and III studies and is mainly to ensure safety and efficacy of drug in humans [8,9]. US Food and Drug Administration (US-FDA) review team examines all the submitted documents related to the drug and makes a final decision. After approval of drug by FDA, manufacturing companies conduct post-market safety monitoring (Phase IV) and post approval studies.

Despite the huge investments and time-consuming processes, the chances of the new drug molecule clearing all the drug approval processes are often negligible [10]. So, the drug manufacturing companies focus on other viable options for drug research. National centre for advancing translational sciences (NCATS), an initiative from of national institute of health (NIH) in the united states of america (USA), defined drug repurposing as “studying the drugs that are already approved to treat one disease or condition to see if they are safe and effective for treating other diseases” [11]. In May 2012, NCATS introduced the program “Discovery of New Therapeutic Uses for Existing Molecules” to focus on new therapeutic indications for the existing drugs, drugs currently in clinical development as well as shelved and discontinued drugs [12]. This approach is also known as repositioning or drug reprofiling. Drug repurposing is a promising approach and is mainly applied for the treatment of rare genetic diseases, and it offers significant benefits to the pharmaceutical industries [13,14]. The usual drug development process may delay the translation of discovery from bench to bedside. This alternate approach overcomes most of the cost and time-consuming hurdles during the drug development process [15]. Drug repurposing was initiated with expanding interest from pharmaceutical organizations and the recognizable proof of different cheminformatics and bioinformatics findings [16]. Out of these, nearly 10% of repurposed drugs were approved by regulatory bodies and 70% are in various stages of clinical development [17].

2. History of drug repurposing

In mid 2000s sildenafil for angina was repositioned to erectile dysfunction and thalidomide for morning sickness was repositioned to multiple myeloma. The success created a big interest in repurposing which resulted in the formation of many repurposing focused startup companies [18]. Many reviews as well as reports of market research confirms repurposing has an important share in the life cycle management of products with an R&D spending of 10–50% [19]. In order to understand the history on the scope of practice of drug repurposing Nancy et al. reported a bibliometric analysis by examining in depth a few drugs. Few examples include chlorpromazine synthesized in 1950 that was indicated for use in controlling mental disorders and as a preoperative medication which was later tried for various diseases like treating whooping cough and symptoms developed in radiation therapy for cancer patients in 1972 [20–22]. Chloroquine was a well-known antimalarial compound synthesized in the year 1934 and was later targeted towards many other diseases including parasitic diseases (before 1960), fever, lupus skin rashes [23,24]. Table 1 summarizes various repurposed drugs which are categorized based on biological activity.

3. Approaches to drug repurposing

Finding out novel disease-drug relationship is a very important issue in drug repurposing. There are various approaches to address the issue such as in silico approaches, biological approaches, experimental, mixed approaches and knowledge based approach. Various approaches to drug repurposing is summarized in Table 2.

3.1. In silico drug repurposing

In this approach, various public databases are utilised and information is gathered from research, clinical trials, reports of label uses, and other published datas. Then, with the help of bioinformatics tools as well as artificial intelligence, interaction networks between drug targets and drugs are identified [97,98]. There are various disease-drug knowledge databases such as ChemBank [99], DrugBank [100], KEGG [101], Pubmed [102], OMIA [103] and genomic databases such as PDB [104], GenBank [105], GEO [106], MIPS [107,108].

The information helps in development of various computational approaches rapidly which are cost effective and have much less barriers [109]. In silico approaches are based on merging and analysing a plethora of information regarding drug-disease relationship [110]. Some are based on gene expression analysis after drug treatment of relevant cell lines. There are various viewpoints

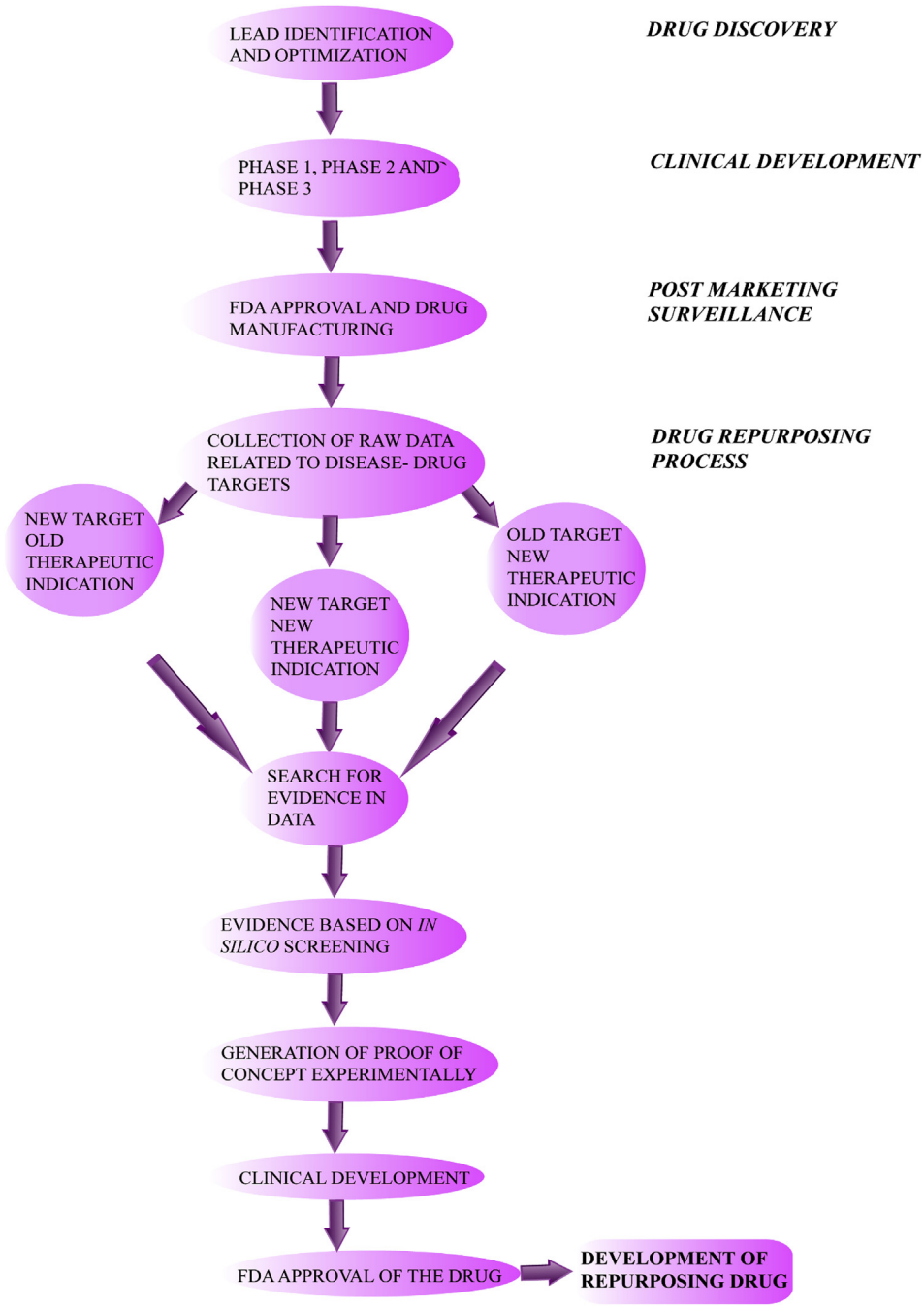


Fig. 1. Various stages of drug development and drug repositioning.

[111–113] such as repurposing based on biological networks employed or hypothesis driven and data driven [113]. Based on methodologies repurposing can be done by text mining [114–126], network-based [127–137], and semantic approaches [138–141].

3.1.1. Text mining approach

In addition to a lot of exploitative information regarding drug repurposing, a large data of biological concept relationships are available from publications. Many are novel and text mining can be employed to mine the information and identify the connections or relationships. Text mining discovers novel information by extracting from several published resources with the help of a computer [142]. Text mining in biology includes, retrieval of relevant information filtered and extracted from literature; biological name entity recognition with the use of controlled vocabularies; biological information extraction and knowledge discovery with the extracted concepts. Relationships between drug-target and drug-disease can also be discovered. Natural language processing techiniques increases the development of tools for text mining and helps finding out repurposable drugs [120,121].

3.1.2. Cluster approaches

Cluster approaches can discover novel drug-target or drug-disease relationships. It is based on the concept, biological entities (protein, drug, disease etc) and network of same module have identical characters. Various modules or groups or sub networks show drug-drug or drug-target or drug-disease relations and are found using cluster algorithms. Few examples are CLIQUE [143],

Table 1
List of repurposed drugs categorized based on biological activity.

Sl.no	Name of drug	Original indication	Novel indication	Reference
Drug Repurposing targeting CNS				
1	Amphetamine	Stimulant	ADHD, Hyperkinesis in children	[25,26]
2	Atomoxetine	Parkinson's disease	ADHD	[25,27–29]
3	Milnacipran	Depression	Fibromyalgia syndrome	[25]
4	Mifepristone	Pregnancy termination	Psychotic major depression, Cushing's syndrome	[25]
5	Duloxetine	Depression, Diabetic Neuropathies	Urinary incontinence, fibromyalgia, musculoskeletal pain, shoulder pain, back pain, osteoarthritis, Diabetic peripheral neuropathy	[30,31]
6	Chlorpromazine	Anti-emetic, antihistamine	Non-sedating tranquillizer	[32]
7	Galantamine	Polio, paralysis and anaesthesia	Alzheimer's disease	[32,33]
8	Ropinirole	Hypertension	Parkinson's disease and idiopathic restless leg syndrome	[25,32,34]
9	Mecamylamine	Hypertension and uncomplicated cases of malignant hypertension	ADHD	[32]
10	Amantadine	Influenza	Parkinson's disease	[35]
11	Infliximab	Crohn's disease	Alzheimer's disease, Different arthritis forms	[30]
12	Perindopril	Hypertension	Alzheimer's disease	[36]
13	Gabapentin	Epilepsy	Neuropathic pain	[37]
Drug Repurposing targeting CVS				
14	Paclitaxel	Cancer	Restenosis	[25,38]
15	Lidocaine	Local anesthetic	Arrhythmia	[25]
16	Aspirin	Inflammation, pain	Antiplatelet	[39]
17	Lomitapide	Lipidemia	Familial hypercholesterolemia	[40]
18	Drospirenone	Oral contraceptive	Hypertension	[36]
19	Fludrocortisone	Cerebral salt wasting syndrome	Hypertension	[36]
20	Pegvisomant	Acromegaly	Hypercholesterolemia	[36]
Drug Repurposing targeting cancer				
21	Thalidomide	Morning sickness	Multiple myeloma	[25,41]
22	Celecoxib	adult rheumatoid arthritis, osteoarthritis	Colon and breast cancer, familial adenomatous polyposis	[32,42]
23	Arsenic	Syphilis	Leukemia	[43]
24	Aspirin	Analgesic, antipyretic	Colorectal cancer	[44]
25	Disulfiram	Alcoholism	Melanoma	[45]
26	Gemcitabine	Antiviral	Cancer	[46]
27	Premetrexed	Mesothelioma	Lung cancer	[47,48]
28	Tretinoin	Acne	Leukemia	[49]
29	Crizotinib	Clinical trials for anaplastic large-cell lymphoma	NSCLC	[50]
30	Imidapril	Hypertension	Cancer cachexia	[30]
31	Leflunomide	Rheumatoid arthritis	Prostate cancer	[44,51]
32	Metformin	Diabetes mellitus	Colorectal cancer, prostate, breast, adenocarcinoma	[44]
33	Methotrexate	Acute leukemia	Hodgkin lymphoma, breast cancer, osteosarcoma	[25]
34	Minocycline	Acne	Glioma, ovarian cancer	[44]
35	Nelfinavir	AIDS	Clinical trials for multiple cancer	[50,52]
36	Nitroxoline	Antibiotic	Bladder, breast cancer	[44]
37	Noscapine	Antitussive, antimalarial,analgesic	Multiple cancer types	[44]
38	Rapamycin	Immunosuppressant	Lymphoma, leukemia colorectal cancer	[44,53]
39	Retinoic acid	Acne	Acute promyelocytic leukemia	[30]
40	Statins	Myocardial infarction	Leukemia, cancer	[44,52]
41	Sunitinib	Renal cell carcinoma, GIST	Gastrointestinal tumor, pancreatic tumors	[50,54]
42	Trastuzumab	HER2-positive breast cancer	HER2-positive metastatic gastric cancer	[50]
43	Valproic acid	Antiepileptic	Solid tumors, leukemia	[44]
44	Vesnarinone	Cardioprotective	Lymphoma, leukemia, oral cancer	[44]
45	Wortmannin	Antifungal	Leukemia	[44]
46	Zoledronic acid	Anti-bone resorption	Breast cancer, prostate cancer, multiple myeloma.	[44]
Drug Repurposing targeting respiratory system				
47	Etanercept	Rheumatoid arthritis	Asthma	[36]
Drug Repurposing targeting GIT				
48	Imatinib	BCR-ABL	GIST	[50]
Drug Repurposing targeting genetic, immunological response				
49	Zidovudine	Cancer	HIV/AIDS	[25]
50	Methotrexate	Cancer	Rheumatoid arthritis	[44]
51	Everolimus	Immunosuppressant	Pancreatic neuroendocrine tumors	[50,55]
52	Furosemide	Edema associated with congestive heart failure	Bartter syndrome	[36]
53	Hydroxychloroquine	Antiparasitic	Anti-arthritic systemic lupus erythematosus	[30]
54	Mycophenolate/ Mycophenolate mofetil	Transplanted organ rejection	Renal symptoms/lupus nephritis of systemic lupus erythematosus	[30]
Drug Repurposing targeting pain and inflammatory diseases				
55	Allopurinol	Tumor lysis syndrome	Gout	[25]
56	Tofisopam	Anxiety-related conditions	Irritable bowel syndrome	[32]
57	Colchicine	Gout	Recurrent pericarditis	[56–58]
58	Propranolol	Hypertension	Infantile hemangioma, Migraine prophylaxis	[59–61]
59	Budesonide	Asthma	Ulcerative collitis	[32,62]
Drug Repurposing targeting metabolic disorders and complications				
60	Sibutramine	Depression	Obesity	[25,30]
61	Bromocriptine	Parkinson's disease	Diabetes mellitus	[63,64]

Table 1 (*continued*)

Sl.no	Name of drug	Original indication	Novel indication	Reference
62	Colesevelam	Hyperlipidemia	Type 2 diabetes mellitus	[65,66]
63	Nortriptyline	Depression	Neuropathic pain	[67,68]
64	Pioglitazone	Type 2 diabetes mellitus	Nonalcoholic steatohepatitis	[69,70]
Drug Repurposing targeting reproductive system				
65	Fluoxetine	Depression	Premenstrual dysphoric disorder	[25,52]
66	Sildenafil	Angina	Erectile dysfunction	[25,30]
67	Dapoxetine	Analgesia and depression	Premature ejaculation	[25]
68	Tadalafil	Cardiovascular disease, Inflammation	Male erectile dysfunction	[32]
69	Apomorphine	Parkinson's disease	Erectile dysfunction	[44]
Drug Repurposing targeting infectious diseases				
70	Thalidomide	Sedation, nausea and insomnia,		
Anti-emetic	Erythema nodosum leprosum in leprosy	[25,30,32,54]		
71	Amphotericin	Antifungal	Leishmaniasis	[71,72]
72	Dapsone	Leprosy	Malaria	[73,74]
73	Miltefosine	Cancer	Cutaneous and visceral leishmaniasis	[75–80]
Drug Repurposing targeting miscellaneous categories of diseases				
74	Minoxidil	Hypertension	Alopecia	[59,81–84]
75	Bupropion	Depression	Smoking Cessation	[25,30]
76	Finasteride	Benign prostatic hyperplasia	Alopecia	[25,32]
77	Lumigan	Glaucoma	Hypotrichosis simplex	[25]
78	Phentolamine	Hypertension	Dental anesthesia reversal agent	[25,85]
79	Eflornithine	Anti-infective	Reduction of unwanted facial hair in women	[32,86]
80	Raloxifene	Prostate and breast cancer	Osteoporosis	[30]
81	Bimatoprost	Glaucoma	Promotes growth of eyelash	[87–91]
82	Doxepin	Depressive disorder	Antipruritic	[30]
83	Naltrexone	Opioid addiction	Alcohol withdrawal	[92–94]
84	Zileuton	Asthma	Acne	[95,96]

CNS: central nervous system.
ADHD: Attention-Deficit/Hyperactivity Disorder.
CVS: Cardiovascular system.
NSCLC: Non-small-cell lung carcinoma.
AIDS: acquired immune deficiency syndrome.
GIST: Gastrointestinal stromal tumors.
HER2: Human epidermal growth factor receptor 2.
HIV: Human immunodeficiency virus.

Table 2
Various approaches to drug repurposing.

Sl.no	Approaches to drug repurposing	Description
1	In silico drug repurposing	Database consists of information gathered from research, clinical trials, reports of label uses, and other published datas
1.1.	Text mining approach	Mine the information and identify the connections or relationships
1.2	Cluster approaches	Can discover novel drug-target or drug-disease relationships based on the concept that biological entities and network of same module have identical characters.
1.3	Propagation approach	Useful in discovering disease-genes, disease-disease, and target- disease relationships based on the concept that information transferred from source node to network nodes and to various sub network nodes.
1.4	Semantics approach	Biological entity relationships are found out from data in medical databases and a semantic network is built also based on existing ontology network and algorithms are developed to discover relationship in the network.
1.5	Databases and resources	Maintained with the purpose of storing, managing and retrieving information. Different types of databases used include pharmacological databases, chemical databases, proteomics databases
2	Biological approaches	Models are developed based on understanding of molecular level pathways and simulate physiological environment of target proteins
3	Experimental approaches	Based on experimentation including targets screening, cell assay, animal model and clinical trials
4	Mixed approaches	It is a mixture of computational observation, biological experiments and clinical testing.
5	Knowledge-based repurposing	Based on the knowledge of researchers and doctors and their capability and skill to interpret observations.

DBSCAN [144], OPTICS [145], STING [146].

3.1.3. Propagation approach

This method can be useful in discovering disease-genes, disease-disease, and target-disease relationships [147,148]. It is based on the concept that information transmit from source node to network nodes and to various sub network nodes. There are local and global approaches. Local approaches extract small information from network, so the prediction may not be successful in some instance [149]. Global approaches extract data from complete network and are better and currently focussed.

3.1.4. Semantics approach

It is extensively used for extracting information and images which can be applied to drug repurposing. In this approach biological entity relationships are found out from datas in medical databases and a semantic network is built also based on existing ontology network and algorithms are developed to discover relationship in the network [108].

3.1.5. Databases and resources

Advancements in biotechnology, bioinformatics and omics techniques (proteomics, genomics, metabolomics, etc) resulted in the development of several databases in biology, chemistry, medicine and pharmacology. These can be utilised for drug repurposing. A list of the various resources are listed out in Table 3.

Table 3
List of various resources for drug repurposing.

Sl.no	Resources	Repurposing Approaches	Website link
1	Pubmed	Text Mining approach	https://www.ncbi.nlm.nih.gov/pubmed/
2	Online Mendelian Inheritance in Animals (OMIA)	Text Mining approach	https://omia.org/home/
3	Drugbank	Pharmacological databases	http://www.drugbank.ca/
4	Drug versus Disease (DvD)	Pharmacological databases	www.ebi.ac.uk/saezrodriguez/dvd
5	Drug Combination Database (DCDB)	Pharmacological databases	http://www.cls.zju.edu.cn/dcdb
6	Drug Map Central (DMC)	Pharmacological databases	http://r2d2drug.org/index.html
7	Side Effect Resource (SIDER)	Pharmacological databases	http://sideeffects.embl.de
8	DailyMed (US FDA)	Medical database	http://dailymed.nlm.nih.gov/dailymed/about.cfm
9	Drugs@FDA Database	Medical database	http://www.fda.gov/Drugs/InformationOnDrugs/
10	FAERS (US FDA)	Medical database	http://www.fda.gov/Drugs/
11	FDALABEL (US FDA)	Medical database	https://labels.fda.gov/
12	ChemBank	Chemical databases	http://chembank.broad.harvard.edu
13	ChEMBL	Chemical databases	https://www.ebi.ac.uk/chembl/
14	ChemDB	Chemical databases	http://www.chemdb.com (Service is currently not available)
15	ChemDB	Chemical databases	http://www.chemdb.com
16	PubChem	Chemical databases	https://pubchem.ncbi.nlm.nih.gov/
17	BindingDB	Chemical databases	http://www.bindingdb.org/bind/index.jsp
18	ChemFrog	Chemical databases	http://www.chemfrog.com (Service is currently not available)
19	Chemicalize (ChemAxon)	Chemical databases	http://www.chemicalize.org
20	ChemSpider	Chemical databases	http://www.chemspider.com
21	Protein Data Bank (PDB)	Proteomics databases	http://www.rcsb.org/pdb/home/home.do
22	Database of Interacting Proteins (DIP)	Proteomics databases	http://dip.doe-mbi.ucla.edu/dip/Main.cgi
23	Human Protein Reference Database (HPRD)	Proteomics databases	http://www.hprd.org/
24	IntAct Molecular Interaction Database	Proteomics databases	http://www.ebi.ac.uk/intact/
25	OCA	Proteomics databases	http://oca.weizmann.ac.il/oca-bin/ocamain
26	Sequence Read Archive (SRA)	Proteomics databases	http://www.ncbi.nlm.nih.gov/Traces/sra/
27	Oncomine	Genomics database	https://www.oncomine.org
28	Online Mendelian Inheritance in Man (OMIM)	Genomics database	http://www.omim.org
29	Pharmacogenomics Knowledge Base (PharmGKB)	Genomics database	http://www.pharmgkb.org
30	ArrayExpress	Genomics database	http://www.ebi.ac.uk/arrayexpress/
31	Kyoto Encyclopedia of Genes and Genomes (KEGG)	Genomics database	http://www.genome.jp/kegg
32	CellMiner	Genomics database	http://discover.nci.nih.gov/cellminer/
33	Database for Annotation Visualization and Integrated Discovery (DAVID)	Genomics database	http://david.abcc.ncifcrf.gov
34	DbSNP	Genomics database	http://www.ncbi.nlm.nih.gov/projects/SNP/
35	Gene Expression Atlas	Genomics database	http://www.ebi.ac.uk/gxa
36	Gene Expression Omnibus (GEO)	Genomics database	http://www.ncbi.nlm.nih.gov/geo
37	Gene Set Enrichment Analysis(GSEA)	Genomics database	http://www.broadinstitute.org/gsea
38	GeneCards Databases	Genomics database	http://www.genecards.org/
39	International Cancer Genome Consortium	Genomics database	https://icgc.org
40	Molecular Signature Database(MsigDB)	Genomics database	http://www.broadinstitute.org/gsea/msigdb
41	Mammalian protein-protein interaction database (MIPS)	Heterogenous networks	http://mips.helmholtz-muenchen.de/proj/ppi/
42	Search tool for interactions of chemicals (STRING)	Biological database/Proteomics databases	http://string-db.org/
43	Biological General Repository for Interaction Datasets (BioGRID)	Biological database	http://thebiogrid.org/
44	Cancer Cell Line Encyclopedia (CCLE)	Biological database	http://www.broadinstitute.org/ccle
45	GPCR-Ligand Database (GLIDA)	Biological approach	http://pharminfo.pharm.kyoto-u.ac.jp/services/glida/
46	NCI Pathway Interaction Database (NCI-PID)	Biological approaches	http://pid.nci.nih.gov/ (Service is currently not available)
47	OPM(membrane proteins)	Biological approaches	http://opm.phar.umich.edu
48	Pathway Commons	Biological approaches	http://www.pathwaycommons.org/about/
49	Psychoactive Drug Screening Program Ki (PDSP Ki)	Biological approaches	https://pdspdb.unc.edu/pdspWeb/
50	Reactome	Biological approaches	http://www.reactome.org
51	Human Metabolome Database (HMDB)	Metabolomics databases	http://www.hmdb.ca
52	Clinicaltrial.gov	Experimental approaches	http://clinicaltrials.gov
53	Library of Integrated Network based Cellular Signatures(LINCS)	Experimental approaches	http://www.lincsproject.org
54	NCGC Database	Experimental approaches	https://tripod.nih.gov/npc/
55	Princeton University MicroArray database (PUMAdb)	Experimental approaches	http://puma.princeton.edu
56	Stanford Microarray Database	Experimental approaches	http://smd.princeton.edu (Service is currently not available)
57	Collaborative Drug Discovery Vault	Mixed approaches	https://www.collaborativedrug.com
58	STITCH (Chemical-Protein Interactions)	Mixed approaches	http://stitch.embl.de/
59	SWEETLEAD	Mixed approaches	https://simtk.org/home/sweetlead
60	The Cancer Genome Atlas (TCGA)	Mixed approaches	http://cancergenome.nih.gov
61	The Connectivity Map (CMap)	Mixed approaches	http://www.broadinstitute.org/cmap
62	The NCGC Pharmaceutical Collection (NPC)	Mixed approaches	http://tripod.nih.gov/npc/
63	TOPSAN	Mixed approaches	http://www.topsan.org (Service is currently not available)
64	DistilBio	Knowledge based approach	http://distilbio.com
65	Proteopedia	Knowledge-based repurposing	http://proteopedia.org
66	Pharmacogenomics Knowledge Base (PharmGKB)	Knowledge based approach	http://www.pharmgkb.org
67	Therapeutic Target Database (TTD)	Knowledge based approach	http://bidd.nus.edu.sg/group/cjttd/

3.1.5.1. Pharmacological databases such as DrugBank, DvD, DCDB, CDD, DrugMap central, network medicine, PharmGKB are very important in repurposing. They extract datas regarding drug properties, drug-biological entities interaction and provides the use of various computational as well as network based tools [100,149–154].

3.1.5.2. Chemical databases such as chembank, ChEMBL, Chem2-Bio2RDF, ChemDB, PubChem provide data regarding chemical structures, 2 D topological fingerprints and 3D conformations. It can predict and find novel drug structures for new indications based on drugs with similar structures and can construct chemical networks [99,155–158]. PubChem is widely used for chemical structures [159].

3.1.5.3. Proteomics databases such as MIPS, PDB, human proteinpedia and HPRD explore protein-protein interactions and can be employed for network-based repurposing [33,36,37,83].. Heterogenous networks such as drug-protein- disease network can be constructed. MIPS is a popular database [107,154,160,161].

Analysing huge amount of literature is essential for drug repurposing, therefore medical literature databases are also important [102,162,163]. PubMed is the most employed with enormous amount of data with over 27 million citations. Properly utilising the data to mine novel information is still evolving.

Various machine learning algorithms along with computational and experimental approaches can improve the potential for repurposing.

3.2. Biological approaches

Systems and network biology help drug discovery by the development of various models which simulate the physiological environment of target proteins and the consequences of modulating them. This approach is very important in targeting multi factorial complex diseases. Polypharmacology approach is also useful as it modulates entire pathways instead of a single target protein. In systems and network biology, models are developed understanding molecular level pathways without losing key details. A multi target approach is also gaining importance to target complex illnesses. Various disease pathway based interaction maps and the effects of modulating various target proteins in model organisms will increase the utilization and influence of systems biology in drug repurposing as well as the drug development process [164].

3.3. Experimental approaches

Experimental approaches include screening of targets [165–169], cell assay [170–173], animal model [174–177] and clinical aspects [55].

3.4. Mixed approaches

There are mixed approaches which confirms computational observation, biological experiments and clinical testing and is very effective for drug repurposing [178–180].

Considering the market, huge number of diseases are in need for new drugs for its treatment. Even in the case of rare diseases more than 6000 to be still explored with research being limited to only 5% of them.

3.5. Knowledge-based repurposing

Drug repurposing can be based on the knowledge of researchers and doctors and their capability and skill to interpret observations. There are chances of serendipity while doing research in some other cases. The first cases of repurposing where mainly by serendipity. Then similar disease conditions which shared altered pathways were explored for combination treatment and to repurpose the drug for its treatment, instead of the originally targeted disease [181].

4. Drug repurposing in various diseases

4.1. Drug repurposing for CNS disorders

Recently Gaspar (2019) reported a novel and promising in silico approach for drug repurposing based on the 44 risk variants published by genome-wide association study (GWAS) for major depressive disorder (MDD). The authors used the online tool Drug Targetor (drugtargetor.com) to evaluate the integration of interactions between drugs and their targets, genome-wide association statistics, and also for genetically predicted expression levels in different tissues. Outside the major histocompatibility complex (MHC) region, 153 protein-coding genes are significantly associated with MDD in MAGMA (which is used to perform pathway analyses) after multiple testing correction. The authors suggests that among these, five are predicted to be down or upregulated in brain regions and 24 are known druggable genes [182].

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two major hotspots of CNS drug research due to the debilitating nature of the disease and dearth of effective treatment options. Lack of better understanding of the underlying mechanisms and involvement of multiple pathophysiological pathways are the major challenges associated with these two neurological diseases. Therefore, drug repurposing gives the hope for finding a successful drug candidate for the treatment of such situations. Tau, a microtubule-associated protein *(*MAP*)* functions in maintaining the assembly as well as disassembly of the microtubules [183]. An aberration in tau phosphorylation disrupting its normal physiology is known to be the cause of neurodegenerative disorders such as AD. Conditions such as hyperphosphorylation or abnormal phosphorylation of tau is known to be caused due to several kinases such as cyclin-dependent kinase 5 (CDK5), microtubule-affinity-regulating kinase (MARK) and glycogen synthase kinase 3 (GSK3) and various signaling pathways such as MAPK and CAMP- dependent protein kinase A respectively, resulting in β,γ-secretases regulation and neuronal apoptosis [184–191].

Silva (2019) reported the anti-aggregating activity of tau proteins by nitrocatechol scaffold, which can be further enhanced by the introduction of bulky substituents at the side chain. A remarkable increase in activity was observed for α-cyanocarboxamide derivative. The authors used docking studies to confirm the activity of these compounds and demonstrated 5-nitro-α-cyanocarboxamide derivatives of caffeic acid and caffeic acid phenethyl ester can effectively inhibit aggregation of tau-derived hexapeptide AcPHF6. which is illustrated in Fig. 2 [192].

Similarly Bourque (2018) provided a detailed review on the protective effect of sex hormones, particularly estrogens, progesterone, androgens and dehydroepiandrosterone on PD through animal models and also in human studies. They suggest that drugs affecting estrogen neurotransmission such as selective estrogen receptor modulators (SERM) or steroid metabolism inhibitors such as 5α-reductase inhibitors could be repositioned for treatment of PD. Sex steroids are also modulator of neurotransmission. This information can be vital in repurposing of drugs for PD [193].

Johnston (2018) provided the scope of drug repurposing in L-DOPA-induceddyskinesia (LID) in Parkinson's disease. The authors approached the subject in three ways such as i*n vivo* phenotypic screening in a hypothesis-free manner; based on analogy to a related disorder; and a hypothesis-driven evaluation of candidates in vivo and in silico screening selection by artificial intelligence.

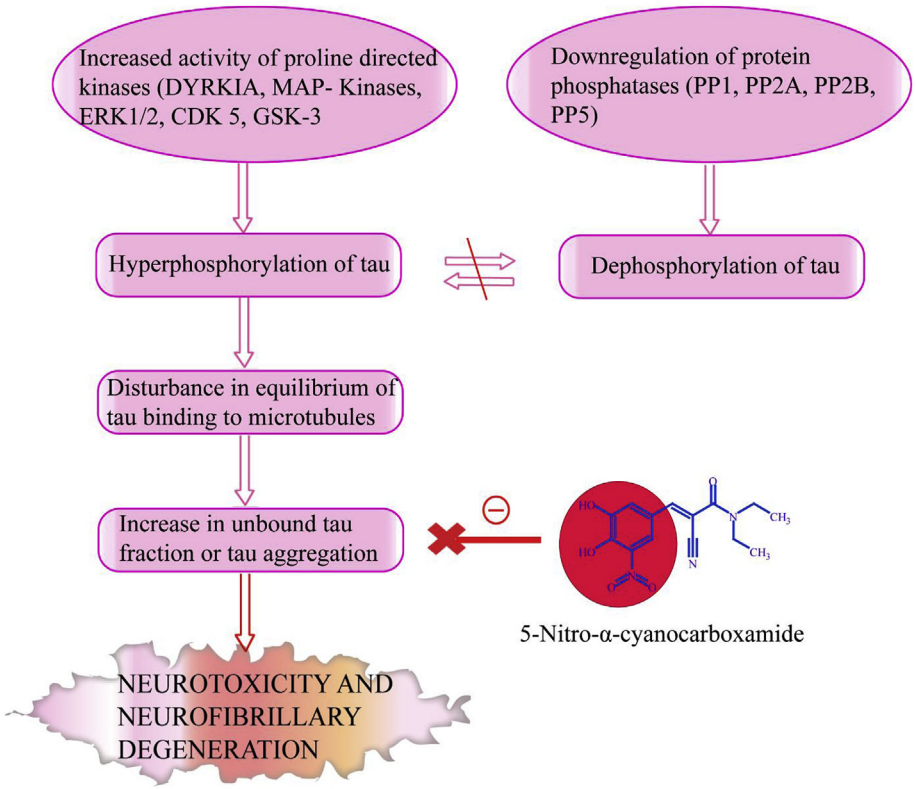


Fig. 2. Anti-aggregating activity of tau proteins by 5-Nitro-α-cyanocarboxamide.

They also provided a case study using IBM-Watson where -a training set of compounds, with demonstrated ability to reduce LID, were employed to identify novel repurposing candidates [194].

Zhu (2019) reported the opportunity for repurposing of omeprazole for oligodendrocyte differentiation and remyelination [195]. Multiple sclerosis is a disease which is immune mediated, hence causes dysregulation of several inflammatory cells and damages the myelin sheath. Proper molecular mechanism is not known so far [196]. The authors identifed omeprazole as a potential, applicable pro-remyelinating drug candidate. The finding was supported by public microarray results from the GEO database, which was analyzed using Connectivity-Map, a database connecting diseases, genes and drugs. This study revealed that the proportion of myelinated axons was found to be increased after omeprazole administration. Thus, it can be concluded that omeprazole is a promising drug candidate for remyelination associated with multiple sclerosis.

Tranfaglia (2018) provided a detailed investigation on the possibilities of drug repurposing for the treatment of Fragile X syndrome (FXS). It is one of the most common inherited causes of intellectual impairment and the major monogenic cause of autism. The authors used Disease-Gene Expression Matching (DGEM) for the repurposing analysis which is a novel and promising approach for drug repurposing. This DGEM study predicted that sulindac could be a potent candidate for fragile X treatment, and subsequent preclinical validation studies have shown promising results. The authored suggest that the use of combinations of available drugs and nutraceuticals has the potential to greatly expand the options for repurposing [197].

4.2. Drug repurposing for cancer

Overcoming the self developed drug resistance of tumours is a huge obstacle in cancer therapy and management. Suitable strategies need to be developed in order to minimise drug resistance and maximize anticancer activity. Discovery and development of anticancer therapeutic agents are deterred by multiple factors including the pharmacology, pharmacokinetics, pathophysiology of the type of cancer and drug metabolism. This major challenge can be successfully resolved by repurposing the drugs since most of the aspects discussed earlier is already known to a greater extent and the drugs are already in existing therapeutic use.

Cyclin-dependent kinase-5(Cdk-5), a threonine or serine kinaseis overexpressed in glioma cells in comparison to the healthy human astrocytes is responsible for neuronal dysfunction and death [198]. Pandey (2019) reported both in vitro and in vivo enhancement of the antitumour activity of temozolomide (TMZ) by the drug Roscovitine (RSV) known to inhibit Cdk-5 [199,200]. This is an interesting result since use of TMZ alone is not effective for gliomas after a while due to the development of drug resistance by malignant cells. The authors observed that TMZ treatment followed by a pre-treatment with RSV significantly enhanced chemo-sensitivity and suppressed the growth of glioma cells by reducing Cdk-5 activity along with simultaneous induction of autophagy and Caspase-3 mediated apoptosis. This study also revealed the reduced expression of Ki67, GFAP and markers of angiogenesis (CD31, VEGF) in case of TMZ + RSV therapy in glioma treatment. CD31, a platelet endothelial cell adhesion molecule-1 (PECAM-1) and vascular endothelial growth factor (VEGF), a cytokine with multiple functions play a key role in endothelial migration as well as proliferation and is highly expressed in glioma [201–206]. The presence of reactive astrocytes in peri-tumoral areas and in areas around blood vessels was completely diminished in TMZ + RSV treated brain sections.

Drug resistance affects many other drug pathways in cancer therapy. Imatinib is a perfect example for this scenario, which is used in the therapy of gastrointestinal stromal tumors (GISTs), one of the most common mesenchymal tumors of the GI tract. Imatinib

loses its desired activity due to development of resistance by tumor cells. Second line therapies involving sunitinib and regorafenib are also not effective due to multiple reasons including cytotoxicity and limited clinical response. Lu (2019) attempted to solve this problem by repurposing cabozantinib for GIST treatment. Authors reported that cabozantinib exhibited higher potency than imatinib against primary gain-of-function mutations of cKIT, a tyrosine kinase receptor which plays the major role in the pathophysiology of GIST by the downstream signaling of MEK/ERK/RAS/RAF, STAT 5 and PI3K/AKT pathways [207–210]. In this study, cabozantinib showed good in vitro and in vivo efficacy in the cKIT mutant-driven preclinical models of GISTs and also displayed a prolonged and sustained effect in the watchful waiting period after the treatment withdrawal. This study increases the scope of carbozantinib as a potent candidate for GIST treatment in future.

Sunitinib is another important chemotherapeutic drug which is a multi-targeted tyrosine kinase inhibitor. It is approved by the FDA for the treatment of renal cell carcinoma (RCC) and imatinib resistant GIST. Recently, Chatziathanasiadou (2019) studied the activity of sunitinib against glioblastoma multiforme (GBM), one of the most dangerous form of malignancy. Treatment of GBM has many limitations due to the unknown pathophysiology of the disease and also due to the variety of physiological factors like poor blood brain barrier (BBB) permeability. The authors successfully developed a validated LC-MS/MS method for the in vitro and in vivo quantitation of sunitinib in glioblastoma cells. There is no report of other study for the estimation of sunitinib uptake in GBM, therefore this finding is quite significant. This method was validated and accredited according to ISO 17025:2005 guidelinein human plasma and successfully applied to cancer patient plasma. The method was successfully adopted to establish a protocol for the evaluation of sunitinib accumulation into M095K glioma cell lines. This work definitely gives some additional momentum in repurposing studies of cancer drugs [211].

Kuenzi (2019) analysed the drug repurposing opportunities for tivantinib, a c-MET inhibitor used in the treatment of acute myeloid leukemia (AML) through a target based approach. The authors repored that tivantinib is a novel glycogen synthase kinase 3 (GSK3α/β) inhibitor that potently kills AML cells. Tivantinib as single agent or combination therapy with ABT-199 may represent attractive new therapeutic opportunities for AML [212]. GSK3α has been already reported as a new target in the treatment of acute myeloid leukemia (AML) by its inactivation via activation of several pathways such as PKB/AKT, S6K, RAS-MAPK and Wnt and hedgehog pathways [212–214]. However, most GSK3 inhibitors lack specificity for GSK3α over GSK3β and other kinases. This work revealed that tivantinib alone or in combination with ABT-199 can effectively inhibit the colony forming capacity of AML bone marrow mononuclear cells. This study gives the possibilities of developing treatment for AML based on tivantinib and further in vivo studies can shed more light on the anticancer potential of the same [212].

There are previous reports of anti-alcoholic drug disulfiram(DSF) being used for cancer treatment. But the mechanism of action of disulfiram remained unknown for a long time and has been explored only recently. Spillier (2019) reported the structure-activity relationships (SAR) of phosphoglycerate dehydrogenase (PHGDH) inhibition by disulfram analogues. This study provided significant insight into the mechanism of anticancer activity of disulfiram by PHGDH inhibition which is illustrated in Fig. 3. This is a result of the oxidation of mutated cysteine 116 residue present in PHGDH which further disrupts the tetrameric state of PHGDH. PHGDH inhibition causes inhibition in proliferation of tumor cells [45].

4.3. Drug repurposing for infectious diseases

Mihai (2019) explored the repurposing of antidepressants consisting of dibenzo[b,e]thiepin scaffold against dengue virus replication. The authors synthesized a series ofdihydrodibenzo[b,e]thiepin derivatives and analysed at 10 μg/mL in HEK293 cells infected with DENV2. In this work, molecular docking studies were also conducted to confirm the tested compounds to DENV2 NS3 helicase and also on dopamine D4 receptor. The objective of the study is to develop a correlation between in vitro and in silico results. It is observed that majority of compounds appear to inhibit only the viral helicase, while others inhibit both helicase and D4 receptors but the mechanism is very complex [215].

Lv (2018) studied target proteins of Japanese encephalitis virus(JEV) for drug repurposing since there is no drugs available for successful treatment. The authors adopted systems biology methods which are a combination of both gene expression data and the data from phenome-wide association studies (PheWAS). By using this efficient approach the authors identified 286 genes which are involved in mechanism of JEV infection [216]. Based on in vivo studies in mice model, it is observed that bortezomib, an anticancer drug indicated for multiple myeloma and lymphoma can lower JEV-induced death in mice, along with alleviating the suffering in JEV infection and also reduce the brain damage possibly by proteasome inhibition [217,218]. This study highlights the possibility of a new drug candidate for JEV treatment.

Another very serious and major zoonotic pathogenic disease is tuberculosis (TB) which is responsible for large scale death and disaster in this class. Thus, identifying a novel and efficient drug is very essential regarding the aggressiveness of TB. Passi (2018) reports a very effective and unique repurposing method based on molecular function correlations among known drug-target pairs to predict novel drug-target interactions. This approach is called 'RepTB' and not much explored anywhere else for drug repurposing strategies. The authors used Network based inference (NBI) method for analyzing a gene Ontology based network containing 26,404 edges, 6630 drug and 4083 target nodes. The study identified four TB targets; FolP1 (Dihydropteroate synthase), Tmk (Thymidylate kinase), Dut (Deoxyuridine 5′-triphosphate nucleotidohydrolase) and MenB (1,4-dihydroxy-2-naphthoyl-CoA synthase) and revealed the similarity in these targets based on examining the drugs. This study is very significant since it introduces a new method for the repurposing giving emphasis on the target proteins of the pathogens [219]. Another study by Singh, A et al., 2019 revealed the stable binding of terlipressin, a vasopressin analogue used for hypotension management with that of EmbC responsible for arabinogalactan synthesis within mycobacterial cell wall [220,221].

Recently Keighobadi (2019) focused the application of 3-(1,2,4-triazol-1-yl)flavanones (TF) against promastigote and amastigote forms of *Leishmania major* (*L. major*). The authors identified 4-chloro derivative (TF-2) having potency about 13 times more than fluconazole against promastigotes. Further analysis using in silico tools showed that TF-2 can be properly incorporated in the active site of parasitic CYP51 and coordinated to the heme. The SAR analysis revealed that the introduction of 4-chloro on 2- phenyl moiety results in the best profile of activity and selectivity. Accordingly, the compound TF-2 prototype can be considered as promising candidate for development of new antileishmanial agents [222].

Staphylococcus aureus has gained significant research interest in drug repurposing studies. The major feature that makes this pathogen for investigation is that it exploits the metabolic pathways of the host organism for the survival which we can investigate with more clarity. Santano (2019) demonstated a host based approach for drug repurposing in *S. aureus* infection. The authors

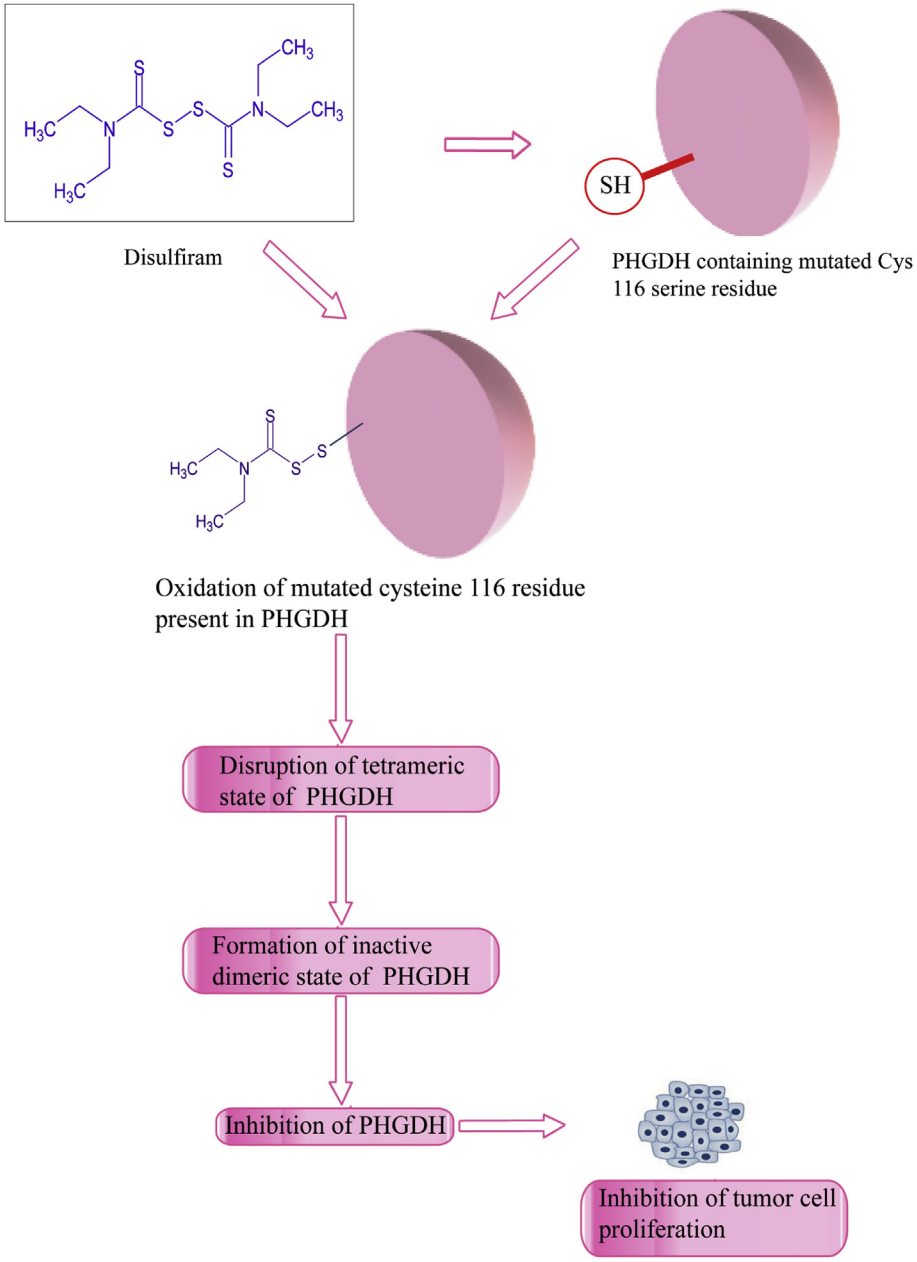


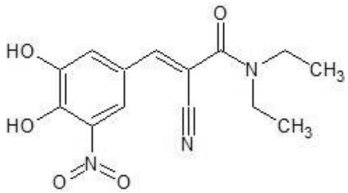
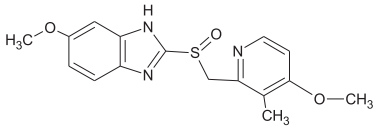
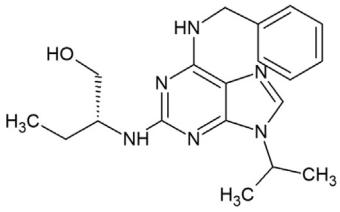
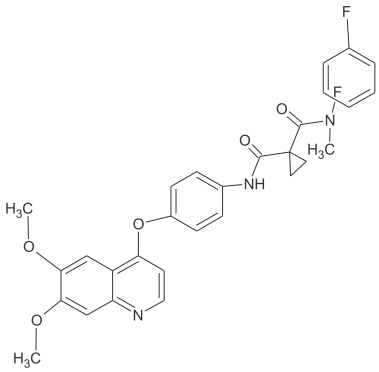
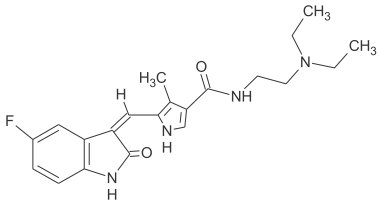
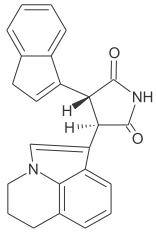
Fig. 3. Disulfiram inhibition of tumor cell proliferation via PHGDH inhibition.

screened 133 host-targeting drugs and found three tyrosine kinase inhibitors; ibrutinib, dasatinib and crizotinib can effectively impair intracellular bacterial survival. Further, ibrutinib significantly increased host cell viability after infection through inhibition of cell invasion and intracellular bacterial proliferation. This study also proposes a putative mechanism of action of ibrutinib based on phosphoproteomics data which involves several host factors, including EPHA2, C-JUN and NWASP [223]. Additionally, Li (2019) also reviewed host based therapeutics were effective against corona virus and influenza virus infections [224].

Similarly, Oleivera (2019) reports the repurposing of non-steroidal anti-inflammatory drug (NSAID) ibuprofen against *S. aureus* infection. The authors used control of adhered cells (2 h) and 24 h old biofilms of *Staphylococcus aureus* for the study and observed that ibuprofen causes metabolic reductions up to 80% and total loss of culturability of adhered cells and 24 h old biofilm. But the drug is not found to be active against antibiotic resistant strains. This aspect requires future investigations for developing another potent drug molecule which can overcome the antibiotic resistant feature of the pathogen [225].

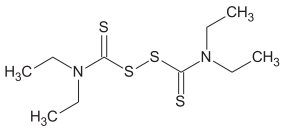
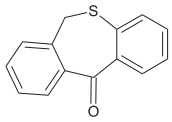
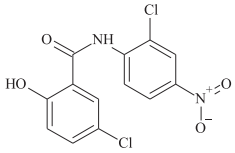
Anticancer drugs are also reported against pathogenic diseases through repurposing. Cisplatin is a major anticancer drug used in the treatment of different kinds of malignancies. Yuan (2018) demonstrated the repurposing of cisplatin against *Pseudomonas aeruginosa*. This study confirms the efficiency of the drug as an antimicrobial agent and kills the pathogens by acting through inhibiting the DNA replication [226,227]. In vitro and in vivo studies also confirm this feature and additionally the drug repressed the type III secretion system (T3SS) of the microbe which is important for the secretion of exotoxins.

Table 4
Recently repurposed drugs in various diseases.

Repurposed Drug	Novel activity/efficacy
CNS disorders	
 5-nitro-α-cyanocarboxamide derivatives	Anti-aggregating activity of tau proteins (AD)
 Omeprazole	Oligodendrocyte differentiation and remyelination associated with multiple sclerosis
Cancer	
 Roscovitine	Individually or in combination with drugs like temozolomide inhibits Cyclin-dependent kinase-5(Cdk-5) there by enhanced chemo-sensitivity and suppressed the growth of glioma cells
 Cabozantinib	Gastrointestinal stromal tumors (GIST) treatment
 Sunitinib	Multi-targeted tyrosine kinase inhibitor (renal cell carcinoma), Treatment of glioblastoma multiforme (GBM)
 Tivantinib	Treatment of acute myeloid leukemia (AML)

(*continued on next page*)

Table 4 (*continued*)

Repurposed Drug	Novel activity/efficacy
 Disulfiram	PHGDH inhibition causes anti- proliferation
Infectious diseases	
 Dibenzo[b,e]thiepin	Inhibit dengue virus replication
Miscellaneous diseases	
 Niclosamide `	Treat pulmonary fibrosis (PF)

Pic (2018) used anthelminthic drug salicylanilide oxyclozanide against *Candida albicans* strains which is found to be clinically resistant. This study found that the drug is active in both sensitive and resistant strains and the antifungal activity of oxyclozanide was enhanced when *C. albicans* grew in nonfermentable carbon sources. The authors reported the possible mechanism of action as disruption of the mitochondrial membrane potential [228]. A list of the various recently repurposed drugs with their chemical structure and efficacy are listed out in Table 4.

4.4. Drug repurposing in other diseases

Patrick (2018) introduced an efficient and successful bioinformatics approach for drug repurposing by using word embedding to summarize drug information from more than 20 million articles and applied machine learning to model the drug-disease relationship. The authors applied drug repurposing approach separately on nine cutaneous diseases including psoriasis, atopic dermatitis, and alopecia areata and eight other immune mediated diseases and obtained a mean area under the receiver operating characteristics of 0.93 in cross validation. They gave emphasis on psoriasis, which is a chronic inflammatory condition of skin that affects more than 100 million people worldwide and using this approach the authors were able to confirm drugs that are known to be effective for psoriasis and to identify potential candidates used to treat other diseases. This work provided an effective algorithm that can be used to identify repurposed drugs for immune disrupted dermatological diseases [229].

Boyapally (2018) reported the repurposing of niclosamide which is an antihelminthic drug for treating pulmonary fibrosis (PF) one of the most deadly lung disease. The authors demonstated the anti-fibrotic potential of niclosamide in TGF-β1 induced in vitro model of pulmonary fibrosis and 21-day in vivo model of bleomycin induced PF respectively. This study showed that niclosamide holds the potential for anti-fibrotic effect by various mechanisms as illustrated in Fig. 4 which includes blockade of epithelial to mesenchymal transition (EMT)as well inhibiting the deposition of extracellular matrix, downregulation of platelet-derived growth factor (PDGF) expression. This leads to reduction in angiogenesis and blockade of WNT/β-catenin signaling thereby inhibiting β-catenin translocation into the nucleus, TGF-β1 production, fibroblasts proliferation and collagen fibers secretion which gives scope for developing successful drug candidate for PF treatment [230–233].

Fang (2018) focuses on drug repurposing for coronary artery disease (CAD) using computational tools. The authors employed in silico approaches by integrating known drug-target interactions, CAD genes derived from the genetic and genomic studies and also through human protein interactomics. This work gives some interesting and novel findings based on reported case studies in which various approved drugs such as Fasudil, Parecoxib, and Dexamethasone and some natural products including Resveratrol, Luteolin, Daidzein and Caffeic acid are efficient in developing drugs for CAD [234].

5. Conclusion and future perspectives

This review focuses mainly on the most recent research advancements in drug repurposing. We have done an analysis of repurposing works and found that most of the recent repurposing falls under anticancer, CNS and pathogenic diseases. Since drug development involves multistage process which is time and money intense, this type of innovative ideas and novel concepts definitely will expedite the drug development process. The repurposed drug is already qualified initial phases of screening and this makes the new objective more feasible and significantly reduces the cost of development.

The process of drug development starts from finding a lead molecule to implementation in the market. But this process is a big scenario which utilizes lot of cost including money and facility and takes very long time of around fifteen years. Repurposing is a vital concept which can overcome these tedious tasks and can boost the drug development process to a significant level. The current repurposing methods include statistical screening of the approved drug and to find the good binding target using in silico methods.

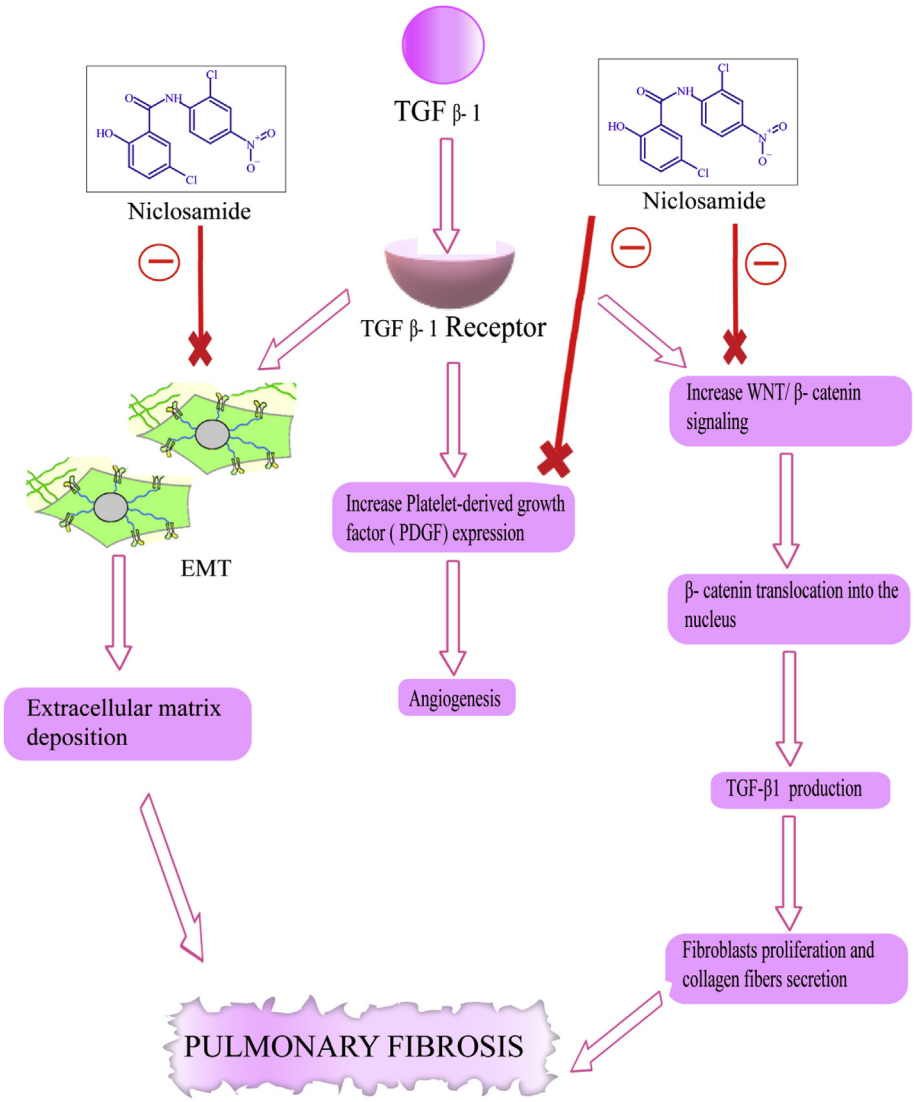


Fig. 4. Mechanisms involved in antifibrotic activity produced by niclosamide.

Since this requires the use of wide library of compounds and data more feasible techniques for repurposing have to be developed. The influence of target is another possibility which is not much explored. The original and repurposed target may have a significant similarity owing to the good binding drug. This aspect has to be exploited at molecular level which can further make the drug repurposing process more efficient and feasible.

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