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DRUG REPURPOSING USING ARTIFICIAL INTELLIGENCE AND NETWORK PHARMACOLOGY FOR NEURODEGENERATIVE DISEASES: A COMPREHENSIVE REVIEW

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ABSTRACT

Alzheimer's disease (AD), Parkinson's disease (PD) and multiple sclerosis (MS) are complex neurodegenerative diseases that are significant public health problems worldwide. Drug repurposing involves using drugs that are already known to be safe for some purpose for a new purpose. It's more likely to be a success than developing novel drugs. Therefore, drug repositioning could serve as a method to hasten the drug discovery process while also conserving both expenditure and time. Artificial intelligence (AI), machine learning (ML), and network-based pharmacology has transformed drug repositioning with integrated analysis of multi-omics data, knowledge biomedical knowledge graphs and real-world evidence (RWE). An assessment of the contemporary state of AI-powered drug repositioning and network-based pharmacology tactics applied to neurodegenerative illnesses comprising major approaches, candidate drugs, mechanisms, and translation barriers. The topic of this paper is the integration of multi-omics, systems biology, and sex-specific considerations in drug delivery tactics. Finally, it outlines potential paths towards clinical translation for the field – in AI related precision medicine and experimental testing.

KEYWORDS: Drug repositioning; Deep learning; Network pharmacology; Multi-omics; Alzheimer's disease.

1. INTRODUCTION

Neurodegenerative illnesses are defined by neuronal malfunction and mortality, leading to a progressive deterioration in cognitive capabilities; Nevertheless, no disease-altering treatments are currently available for these illnesses.[5,6,15] There are certain problems in the conventional process for discovering drugs, since they have a high risk and long process and long process and also due to the complex nature of these illnesses.[2,9,11]

The process of drug repurposing enables the repurposing of current medicine using up-to-date pharmacokinetic, safety, and manufacturing data to facilitate novel therapeutic objectives.[13,20,24] As a result, the integration and interpretation of complicated biomedical data, like genomes, transcriptomics, proteomics, metabolomics, and actual-world data (RWE) has been made possible by the creation of AI and network-based pharmacology, thereby supporting drug repositioning.[2,5,15,25] The main purpose of this article is to make a comprehensive synthesis on the methods of drug repositioning based on AI and network-based pharmacology in neurodegenerative diseases, taking Alzheimer's disease as an example.

2. REPOSITIONING DRUGS

Target-focused and disease-focused drug repurposing approaches are the two main ones.[5,7,15] Although drug repurposing techniques, which target medications that work on frequent molecular targets found in several illnesses, concentrate on medications, disease-specific strategies use shared biological pathways or pathophenotypes across disease.[5,15]

For instance, sildenafil, which was first authorized for pulmonary arterial hypertension and erectile dysfunction,

has been found promising in Alzheimer's therapy based on its manipulation of phosphodiesterase activity and neuroprotective processes.[5,13,15] Likewise, antidiabetic medications like as metformin and GLP-1 receptor agonists (such as as semaglutide and liraglutide) have been repurposely repurposed to target insulin pathway irregularities in Alzheimer's disease.[3,15,26,27] Network-based pharmacology provides an extra level of explanation by demonstrating the links between drugs, targets, and illnesses in biological networks, which helps to comprehend multi-target medications and polypharmacological effects.[5,15,19] It is especially relevant for diseases of the central nervous system, which are characterized by complex pathophysiology involving multiple molecular mechanisms including the progression of amyloid-beta aggregation, tau hyperphosphorylation, neuroinflammation, mitochondrial dysfunction and degeneration of synapses.[1,3,15]

3. DRUG REPURPOSING USING AI

AI, ML and DL have revolutionised drug repositioning by leveraging the analysis of huge amounts of multi-omics and clinical data, which can then be used to predict drug-disease relationships, drug-target interactions and combinations of drugs to produce synergies.[2,5,15,25] Graph neural networks, knowledge graphs, NLP and generative AI techniques are used by prominent AI platforms like DeepDrug, COMIC, DrugPipe, and AGATHA to discover candidates for repurposing.[2,5]

3.1 Data integration and AI-compatible databases

The major datasets required to ensure successful applications of AI include those that contain data related to chemical, genomic, proteomic, pathway and clinical information – all of which are data-rich and multimodal.[5] Model training and validation necessitate appropriate information, which could be obtained from public databases, such as ChEMBL, DrugBank, UniProt, KEGG, STRING, and DisGeNET.[5] Additionally, real-life health data (RWDs) gathered from electronic health records (EHRs) and insurance claims enhance clinical trial simulation and testing of the repurposing ideas.[5,15]

3.2 Optimization in AI and deep learning

Even though the structure of molecules is not known, molecular fingerprints, similarity matrices and sequence data like SMILES are used by ML techniques (supervised, unsupervised, semi-supervised) for prediction of drug target interaction.[5,15] The deep learning models can improve the power of the prediction by dealing with the unstructured data like molecular pictures and 3D structures. The multiformat learning frameworks can be used to enhance drug property and target interaction prediction by integrating various data types.[5]

3.3 Approaches of network-based and knowledge graphs

AI-based approaches to network analysis, such as protein-protein interaction (PPI) network analysis, repurposable drugs-disease-target graph, and multilayer biological networks, suggest the mechanistic plausibility of repurposable drugs.[5,15] This makes knowledge graph embeddings and explainable AI (XAI) technologies more interpretable, and reliable.[5]

4. NEURODEGENERATIVE DRUG REPURPOSING WITH NETWORK PHARMACOLOGY AND SYSTEMS BIOLOGY

Network-based Pharmacology identifies drugs' polypharmacological effects by mapping drug interactions in disease specific networks of biology with help of systems biology.[15,19] This is critical to neurodegenerative diseases with complex aetiology.

4.1 Multi-omics data integration

Combination of genomics, transcriptomics, proteomics, metabolomics and epigenomics provides a detailed understanding of disease action and drug action.[2,3,5] There are shared pathogenic pathways observed in illnesses of AD, PD and MS that have been found in AI-based multi-omics analyses, such as the inflammatory processes of oxidative stress, mitochondrial dysfunction and neuroinflammation processes.

4.2 Systems pharmacology models

Drug repositioning is helped in precision drug repositioning using frameworks from systems-based pharmacology that simulate the interactions between drugs, their targets, pathways operating in biological systems, and diseases.[2,5] Dynamic network simulation tools such as PETS can be used to simulate and predict drug efficacy and possible off-target effects for neurodegenerative diseases.[2]

4.3 Case example

A case example is provided to discuss the mechanism, clinical use, and precautions of drugs for Alzheimer's Disease: SGLT2 Inhibitors. Network-based pharmacology and Molecular docking analysis have identified Sodium-glucose cotransporter-2 (SGLT2) inhibitors such as canagliflozin as possible drugs in AD targeting proteins involved in amyloid processing and neurodegeneration processes like GAPDH, GSK3B and APP.[4] To validate the repositioning potential of canagliflozin, the binding of canagliposin to GAPDH was checked by molecular dynamics simulations and found stable.

5. DRUG REPURPOSING TOOLS FOR AI AND NETWORK PHARMACOLOGY

Table 1: Tools in AI and Network pharmacology for drug repurposing.

Tool name	Description
Cloudscreen (AI)	Structural modelling and machine learning platform based on integrated 3D/1D data to evaluate biomolecule efficacy.[29]
AI-DrugNet (AI)	Prediction of drug-target pairs based on deep learning on the network for neurological disorder drugs.[30]
REx (AI)	A reinforcement learning agent that finds explainable paths in large scale biological knowledge graph.[31]
AMGAT-DR (AI)	Uses multi-layer graph attention and heterogeneous embedding to maximize the drug effectiveness and safety profiles.[32]
DTINet (Network Pharmacology)	Combines heterogeneous biological networks to discover low dimensional vector representations to predict drug-target interactions.[33]
NeoDTI (AI & Network Pharmacology)	A neural integration framework which integrates multiple information networks of drugs, genes and diseases to generate novel candidate.[34]
CMap / L1000 (Network Pharmacology)	In the 'Connectivity Map', the study of gene expression signatures allows the mapping of drugs, genes and diseases to biological networks.[35]
PharmDB (Network Pharmacology)	An innovation database platform built specifically for the analysis of complex interactions of drugs and targets with disease.[36]
BATMAN-TCM (Network Pharmacology)	Specific tool to analyze multi-target action of complex formulations (commonly used in TCM) in biological networks.[37]
DeepChem (AI)	Standardized deep learning tools for chemistry, genomics and drug discovery in a comprehensive library in python.[38]

6. DISCOVERY OF DRUG CANDIDATES USING AI AND NETWORK PHARMACOLOGY

6.1 Alzheimer's disease

Several FDA-approved and research-oriented medicines have come up as repurposing candidates for AD using AI and network-based pharmacology:

- Ibudilast: A phosphodiesterase inhibitor that has anti-inflammatory and neuroprotective activities, reducing amyloid pathology and microglial activation.[3]
- Timapiprant: A selective antagonist of the prostaglandin D2 receptor that targets neuroinflammation and microglial activation.[3]
- RG2833: A histone deacetylase (HDAC) 1/3 inhibitor that enhances synaptic plasticity and cognitive function, particularly in females.[3]
- Diazoxide/Dibenzoylmethane (DZ/DIB): Medications that modulate mitochondrial function as well as tau pathology.[3]
- BT-11: A research-oriented drug that targets immunometabolic pathways with cognitive advantages primarily seen in males.[3]

6.2 Diabetes medications and neurodegeneration

Type 2 diabetes mellitus (T2DM) is associated with AD through common insulin signaling dysfunctions.[1,3] GLP-1 analogues (e., liraglutide, exenatide) as SGLT2 inhibitors have shown neuroprotective effects and are being examined clinically for AD.[1,3,4]

6.3 Antihypertensive agents

Angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) have demonstrated potential in the treatment of AD by lowering amyloid accumulation, neuroinflammation, and enhancing cognitive results.[1]

6.4 Antibiotics and retinoid-based therapy agents

A promising medicine to treat Alzheimer's disease-Minocycline, a tetracycline antibiotic, and retinoid-based therapies have shown potential in preclinical models by reducing amyloid aggregation as well as modulating neuroinflammation.[1]

6.5 Sex-specific mechanisms and therapeutic considerations

In recent years, the roles played by sex differences in the pathways of pathophysiological events in neurodegenerative diseases and how these differences affect their treatment have been highlighted.[3] For example, females of the TgF344-AD rats are cognitively resistant in the face of amyloid accumulation, whereas there will be increased neuronal loss, and increased microgliosis in males. Drugs such as RG2833 and BT-11, which are more effective in males than in females. Thus, it emphasises need for specific and individualised treatment regimens.[3]

7. KEY CHALLENGES AND FUTURE PERSPECTIVES

7.1 Experimental and clinical validation

Although AI and network-based pharmacology have improved the processes of drug repositioning, experimental and clinical validation is essential to confirm the drug's predicted activities on the target and in experiments to prove its effectiveness in the clinic. The use of real-world data and EHRs for clinical trial emulation complements the preclinical results, by evaluating real-world drug safety and efficacy.[5]

7.2 Data transformation and data dimension

Multi-omics and clinical data analysis come with challenges of data sharing limitations, model

transparency challenges, and difficulties. There are two new strategies namely federative learning features and AI explanation, used to make the data more transparent and private.[5]

7.3 Precision medicine

Integrating AI-guided multi-omics and network-based pharmacology helps advance precision medicine by identifying patient subpopulations most likely to benefit from particular repositioned drugs, accounting for factors like sex, genetic background, and disease state.[2,3,5]

8. CONCLUSION

AI and network pharmacology create a powerful combination to advance drug repositioning strategies for neurodegenerative diseases, aiding in comprehensive, data-driven drug identification and understanding of their mechanisms. Repurposed drugs with potential vary across various classes such as anti-inflammatory agents and antidiabetics, antihypertensives and epigenetic modulating agents. Incorporation of sex-specific particularities and multi-omics adds further precision in therapeutic approaches.

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