Preface

Drug repurposing is a method for discovering new applications for FDA-approved or experimental drugs beyond their scope of original medical indication. Due to the excessive rates of attrition, substantial costs and slow pace of new drug discovery and development, there is recently a surge in drug repurposing. In this thesis we aim to use drug repurposing methodologies for identifying some possible repuposed drugs for neuroprotection in brain dysfunction, such as Alzheimer's disease (AD) and neurotropic infectious diseases like Japanese Encephalitis (JE) and COVID-19. The current increase in life expectancy and lack of viable treatments for AD, JE and COVID-19 raise considerable public health concerns. We have also implemented a polypharmacology framework, which helps us replace the customary “one-drug/one-target” model with a “multidrug/multitarget” model. We all are aware that the above-mentioned diseases are multifaceted involving multiple pathophysiological manifestations, and hence therapeutic agents should target those multiple pathways simultaneously for effective therapeutic efficacy. Therefore, we have also identified some repurposed drug combinations for Alzheimer's disease. Moreover, we utilized network pharmacology approach to identify the various mechanisms through which the repurposed drugs could be useful in treating these diseases.

Our first study investigates some repurposed hepatomodulatory drugs (rifampicin, metformin, 24-hydroxycholesterols, resveratrol, cilostazol) and the role of the liver in Alzheimer's disease (AD) by examining the transport processes of amyloid-beta (Aβ). We have found that increasing the expression of genes ATP-binding-cassette-transporter (ABCA1) and Stearoyl-CoA-desaturase (SCD) can minimize Aβ production, while increasing ABCG2 and MDR1 expression can enhance clearance. We also identified an intestinal enterocyte with a receptor-like apical sodium-dependent bile acid transporter (ASBT) that may reabsorb amyloid-beta from intestinal contents back into the blood. We have used molecular docking and molecular dynamic simulation to target these receptors, resulting in improved fecal clearance and reduced amyloid-beta formation. Network pharmacology and synergism analysis confirmed our theory and helped determine the optimal combination of repurposed medications. Clinical trials also supported the conclusions regarding these candidate drugs.

Liver and lipid homeostasis are crucial in AD, with cholesterol metabolism in the liver affecting Aβ clearance through cerebral vasculature. Ageing-induced hepatic dysfunction can impair cholesterol metabolism, reducing the availability of cholic-acid (CA) in the brain. CA has neuroprotective characteristics in preclinical investigations of Alzheimer's disease. In our second study, we have analyzed serum cholic-acid concentrations in 182 healthy and 136 Alzheimer's disease subjects. Statistical analysis showed that serum cholic acid in Alzheimer's subjects significantly decreases to half of the value in normal subjects. Brain amyloid load is significantly higher in Alzheimer's subjects, and total and regional cerebral blood flow diminishes substantially to around 50%. Regression analysis revealed a significant interaction between cholic-acid levels with amyloid load and CBF. We also undertook Granger causation analysis to determine cause-effect relationships whereby higher serum cholic acid causatively reduces brain Aβ. The study highlights the central importance of the body's basic metabolic system, the hepatobiliary framework, and its metabolites in AD. Indeed, repositioned pharmacological modulation by cholate derivatives or cholic acid may have appreciable potential as a novel therapeutic approach to Alzheimer's disease.

Our next study validates our previous research on hepatotropic drugs that improve brain amyloid beta clearance through the liver into bile and feces. Our MRI tractography analysis revealed that tracts associated with the spreading Braak stages were primarily involved in the limbic and frontoparietal networks. The predicted hepatotropic drugs improved these networks, which were compromised in Alzheimer's patients. Our investigation also identifies the diffusivity parameters in brain networks that impact AD and drug treatments. MRI-DTI parameters are normalized by the repurposed drug therapy. The white matter integrity of the tracts in AD was evaluated in comparison to control subjects, which indicates that that white matter degeneration could be an early marker of AD pathogenesis. Analyzing the alterations in the microstructural organization of region of interests may be helpful in AD diagnosis. The study suggests that hepatotropic drugs may have promising potential as AD therapeutic modality, with clinical corroborations also being furnished in our investigation.

Our final study identified some possible repurposed drugs and phytochemicals for treating neurotropic viral infections. Recent investigations have shown that acute respiratory failure and neuroinfection may result from systemic invasion caused by pulmo-neurotropic viruses. These viruses include Japanese encephalitis, SARS-COV2, HIV, and SIV. Treatment with tetracycline and cephalosporin is effective for treating these diseases, but viral resistance to these drugs is a significant public health crisis. To investigate the antiviral potency of alternative drug like secondary metabolites, such as phytochemicals, our study was conducted to examine the therapeutic effectiveness of phytochemicals like podophyllotoxin, chlorogenic acid, naringenin, and quercetin in neurotropic viral infections.

Furthermore, MRI scanning and fiber-tractography were used to analyze the connections between cranial nerves and the brain-stem/limbic region. A human clinical trial evaluation was conducted to develop a quantitative model of antiviral pharmaceutical intervention. Docking studies were performed to identify the binding affinity of the phytochemicals toward antiviral targets, such as host receptors and main proteases of SARS-COV2 and NS3-Helicase/Nucleoside triphosphatase of Japanese encephalitis virus.

The potential mechanism of action of these phytochemicals was determined using network pharmacology analysis.

The results of human MRI-tractography investigation revealed fiber connections between the olfactory nerve and the limbic area, with phytochemicals showing similar binding affinities for viral receptors and host cell receptors. The phytochemicals successfully inhibited neuroinflammation caused by the cytokine storm, a significant pathogenic route of disease aggravation. The patient survival curve under antiviral therapy is explained by a systems biology-based double-hit mathematical bi-exponential model, providing a quantitative clinical framework of secondary metabolite action on virus and host cells. As a result of increasing viral resistance to antibiotics, new phytochemicals with clinical therapeutic potential for neurotropic virus infection have been thus identified by us. Our investigation defined the anatomical route and quantitative formulation of the mechanism of antiviral activity using human MRI scans and clinical trial data.

The work embodied in this thesis has been presented under the following chapters:

Chapter 1: The chapter provides an introduction to drug repurposing for neuroprotection (neurodegenerative disorder as Alzheimer's disease and neuroinfection as Japanese Encephalitis, COVID19), along with advantages and approaches of drug repurposing.

Chapter 2: The chapter deals with the detailed drug repurposing, role of liver and need for combination therapy in Alzheimer's disease. The literature review, hypothesis and work plan are also incorporated.

Chapter 3: The chapter deals with the investigation on our proposed repurposed drugs for Alzheimer's disease.

Chapter 4: The chapter introduces hepatometabolic agents, which may play a significant role in the treatment of Alzheimer's disease. The literature review, hypothesis and work plan are also incorporated.

Chapter 5: The chapter deals with neuroimaging, biochemical investigation, along with granger causation analysis of hepatometabolic agents for Alzheimer's disease.

Chapter 6: The chapter introduces the framework of MRI tractography, together with neuroanatomical and clinical trial verification for our hepatomodulatory drugs for AD.

Chapter 7: The chapter deals with neuroanatomical circuit-based drug repurposing in different neurobiological subtypes of Alzheimer's disease. In this chapter we discussed about our repurposed drugs which can target different neuroanatomical brain networks to provide an effective therapeutic intervention for the different anatomical variants of AD.

Chapter 8: The chapter introduces the therapeutic efficacy of antibiotics and phytochemicals in treating neurotropic viral infection mainly Japanese Encephalitis and COVID19. The literature review, hypothesis and work plan are also incorporated.

Chapter 9: The chapter deals with the investigation on our proposed repurposed drugs for neurotropic viral infection.

Chapter 10: This chapter outlines the summary and conclusions of the research work Undertaken in this thesis.

Chapter 11: The references, used to carry out the research work, are presented in this chapter.

An appendix consisting of the additional supporting information and a list of publications of the author in neuroprotection are included.