

Table of Contents

List of Figures.....	xiii
List of Tables	xxi
List of abbreviations	xxiii
Preface.....	xxv
Chapter 1	2
1. Introduction	2
1.1 Drug Repurposing	2
1.1.1 Advantages of drug repurposing.....	2
1.1.2 Historical evidence of drug repurposing with the year of approval	3
1.1.3 Drug repurposing approaches	4
1.1.3.1 Computational Approaches	4
1. Genetic Association.....	4
2. Neuroimaging and Tractography	5
3. Pathway Mapping.....	6
4. Molecular Docking	6
5. Molecular Dynamics Simulation	6
6. Retrospective Clinical Analysis.....	6
1.2 Drug Repurposing in Alzheimer's disease.....	8
1.2.1 Alzheimer's disease statistics.....	8
1.2.2 Alzheimer's disease pathophysiology	8
1.2.3 Metabolism of amyloid- β	9
1.2.4 Cholesterol and amyloid- β	9
1.2.5 Hepatobilliary-Enterohepatic circulation of cholesterol and therapeutic intervention	10
1.2.6 Hepatobilliary-Enterohepatic circulation of amyloid- β and therapeutic intervention.....	10
1.3 Drug Repurposing in Neurotropic Viral Infection	10
1.3.1 SARS-COV2 and JE statistics	10
1.3.2 SARS-COV2 and JE causing CNS infection	11
1.3.3 Pathophysiology of SARS-COV2 and JE	12
1.3.4 Biological secondary metabolites as a therapeutic approach to viral infection	13
Chapter 2	16
2. Drug repurposing in Alzheimer's Disease.....	16
Literature review, hypothesis and work plan:	16

2.1 Formulation of system analysis: Hepatobiliary-Enterohepatic circulation of amyloid-beta.....	16
2.2 Receptors implicated in the hepatobiliary - enterohepatic circulation of Aβ17	
2.2.1 ABCG2 and ABCB1/MDR1 receptor.....	17
2.2.2 Liver X Receptor-beta.....	17
2.2.3 Apical sodium-dependent bile acid transporter (ASBT) receptor.....	18
2.2.4 Bile Salt Export Pump (BSEP) receptor	18
2.3 Framework of the investigation.....	20
Chapter 3	22
3. In-Silico investigation on repurposed drugs for Alzheimer's disease.....	22
3.1 Introduction	22
3.2 Materials and methods.....	23
3.2.1 Molecular docking	23
3.2.1.1 Docking with amyloid-beta.....	23
3.2.1.2 Docking with repurposed drugs	23
3.2.2 Molecular dynamic simulation.....	24
3.2.3 Network pharmacology.....	24
3.2.3.1 Data formulation	24
3.2.3.2 Identification of differentially expressed genes (DEGs).....	25
3.2.3.3 Pathway enrichment analysis	25
3.2.3.4 Identification of hub-genes and sub-network analysis.....	25
3.2.3.5 Ingenuity pathway analysis (IPA).....	25
3.2.3.6 IPA drug pathway procedure - identifying overlapping molecules	26
3.2.4 Synergy testing.....	27
3.3 Results.....	27
3.3.1 Docking study	27
3.3.1.1 Molecular docking of amyloid beta	27
3.3.1.2 Molecular docking of repurposed drugs	30
3.3.2 Molecular simulation dynamics results.....	33
3.3.2.1 Root mean square deviation.....	33
3.3.2.2 Root mean square fluctuation	33
3.3.2.3 The radius of gyration (Rg) and solvent accessible surface area (SASA)	34
3.3.2.4 Protein-ligand contact	38
3.3.3 Network pharmacology analysis.....	43
3.3.3.1 Identification of differentially expressed genes (DEG)	43
3.3.3.2 Gene ontology analysis	44

3.3.3.3 Interconnected pathway analysis of proposed drugs and receptors	48
3.3.4 Validation Analysis for clinical efficacy	49
3.3.5 Combination therapy	50
3.4 Discussion	52
3.5 Conclusion	55
Chapter 4	58
4. Hepatometabolic agents as a therapeutic intervention in Alzheimer's disease.....	58
Literature review, hypothesis and work plan:.....	58
4.1 Hepatometabolic agents and Alzheimer's Disease	58
4.2 Causation Analysis	59
4.5 Imaging Modalities	60
4.6 Framework of the investigation.....	61
Chapter 5	64
5. Neuroimaging, Biochemical investigation with causal analysis of hepatometabolic agents for Alzheimer's disease.....	64
5.1 Introduction	64
5.2 Materials and methods	65
5.2.1 Scanning of Alzheimer's Disease patients	65
5.2.2 Serum Cholic Acid Concentration Analysis.....	65
5.2.3 Scanning of healthy normal subjects	66
5.2.4 Imaging investigations.....	66
5.2.5 Amyloid Load: Florbetapir PET Data Acquisition and Processing.....	66
5.2.6 Cerebral Blood Flow - MRI Arterial Spin Tagging analysis.....	68
5.2.7 Causation Analysis	69
5.2.7.1 Causality relationship between cholic acid and amyloid load	70
5.2.7.2 Causality relationship between amyloid load and cerebral blood flow	71
5.2.8 Statistical Analysis	72
5.3 Results.....	73
5.3.1 Serum cholic acid concentration in AD patients is half of normal subjects	73
5.3.2 Cerebral blood flow in Alzheimer patients is half of normal subjects	73
5.3.3 Higher amyloid-beta load in Alzheimer's disease	75
5.3.4 Correlation between amyloid load (SUVR) and CBF with MMSE	76
5.3.5 Receiver Operating Characteristics Curve	76
5.3.6 Interaction of Cholic acid, Amyloid beta and Cerebral blood flow	79
5.3.7 Cholic acid causatively influences Amyloid- β load	79
5.3.8 Amyloid load causatively influences Cerebral blood flow.....	80

5.3.9 Mechanistic substantiation of inhibition of amyloid- β formation by cholic acid	81
5.3.10 Mechanistic corroboration of inhibition of cerebral blood flow by amyloid- β	83
5.3.11 Normal subjects - Relationship of Mental status with A β load and with CBF	84
5.3.12 Relationship of Amyloid load to Cerebral Blood Flow in Normal subjects	84
5.4. Discussion	86
5.4.1 Primary findings.....	86
5.4.2 Alteration of cholic acid level influences cognitive impairment	87
5.4.3 Cholic acid as causative factor in decreasing Amyloid load.....	87
5.4.4 Amyloid beta causatively affects and inhibits cerebral blood flow	88
5.4.5 Healthy subjects: No relationship between amyloid load and cerebral blood flow. Concentration Threshold effect.....	88
5.4.6 Diagnostic and therapeutic implications	89
5.5 Conclusion	92
Chapter 6	96
6. MRI tractography, neuroanatomical and clinical trial verification for hepatomodulatory drugs for Alzheimer’s Disease therapy.....	96
Literature review, hypothesis and work plan:	96
Chapter 7	100
7. Neuroanatomical Circuit Based Drug Repurposing in different biological sub-types of Alzheimer’s Disease	100
7.1 Introduction	100
7.2 Materials and methods.....	101
7.2.1 Analysis of clinical trial findings and neuroimaging scans.....	101
7.2.2 DTI Data acquisition.....	101
7.2.3 Tractography Analysis	102
7.2.4 Genetic Association Analysis	103
7.3 Results.....	103
7.3.1 Clinical trial analysis.....	103
7.3.2 Deterministic Tractography	105
7.3.3 Microscopical histological validation with Braak Staging	107
7.3.4 Diffusivity parameters alteration in Alzheimer’s Disease	109
7.3.5 Gene Expression Analysis	112
7.3.6 Identification of expression of the genes	113
7.3.7 Assessment of expression of the genes:.....	114
7.4 Discussion	116
7.5 Conclusion	119
Chapter 8	122

8. Repurposed antibiotics and phytochemicals for therapeutic intervention in neurotropic viral infection	122
Literature review, hypothesis and work plan:.....	122
8.1 Repurposed antibiotics and phytochemicals in Central Nervous System viral infection	122
8.2 Rationale of using phytochemicals as therapeutic intervention.....	122
8.3 Predicted pathway for virus transmission.....	123
8.4 Hypothesis and Framework of the Investigation.....	124
8.5 Our mathematical formulation of system analysis: Double hit model	126
Chapter 9	130
9. Computational biology-based investigation on repurposable drugs for CNS infection	130
9.1 Introduction	130
9.2 Materials and methods.....	132
9.2.1 Image Acquisition	132
9.2.2 Fiber Tracking with DSI Platform.....	132
9.2.3 Docking Studies.....	133
9.2.3.1 Retrieval of the Target Protein	133
9.2.3.2 Selection of Ligands and Its Optimization	133
9.2.3.3 Molecular Docking Procedure.....	133
9.2.4 Network Pharmacology	135
9.2.4.1 Retrieval of the Target Genes.....	135
9.2.4.2 Network Construction and Topological Analysis	135
9.2.4.3 Gene Ontology (GO) and KEGG Enrichment Analysis of Targets.....	135
9.3 Results.....	136
9.3.1 MRI Tractography Analysis	136
9.3.1.1 Connection Between Brain Stem and Gustatory Nerves.....	136
9.3.1.2 Connection Between Limbic System and Olfactory Nerves	139
9.3.2 Docking Study.....	140
9.3.2.1 Binding Sites of ACE Receptor.....	140
9.3.2.2 Interaction Between ACE2 Receptor and SARS-COV2.....	142
9.3.2.3 Interaction Between ACE2 Receptor with Tetracycline Ligands and Phytochemicals.....	143
9.3.2.4 Interaction Between SARS-COV2 Main Protease with Tetracycline Ligands and Phytochemicals.....	147
9.3.3 Validation of Our Data	149
9.3.3.1 Docking Results with Japanese Encephalitis.....	149

9.3.3.2 Modeling with clinical trial findings.....	151
9.3.4 Network Pharmacology Analysis.....	153
9.3.4.1 Targets Prediction Results	153
9.3.4.2 Gene–Gene Interaction Analysis	154
9.3.4.3 Gene Ontology and KEGG Enrichment Analysis for Targets	161
9.4 Discussion	162
9.5 Conclusion	165
Chapter 10	168
10.1 Summary of major findings	168
10.2 Future scope of our research.....	170
References	174
APPENDIX.....	189
List of publications.....	215