Applications of Artificial Intelligence in Discovery and Development of Therapeutics for the Treatment of Alzheimer's Disease

Thesis submitted in partial fulfilment for the Award of Degree

Doctor of Philosophy

By

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Date:

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List of abbreviations

Abbreviation	Full Form
3D	Three dimensional
ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
AI	Artificial intelligence
Aβ	Amyloid-β
APP	Amyloid precursor protein
AS	Anionic site
ATP	Adenosine triphosphate
AUC	Area under the curve
BBB	Blood-brain barrier permeability
BChE	Butyrylcholinesterase
BLAST	Basic local alignment search tool
CaMKII	Ca^{+2}/calmodulin dependent protein kinase II
CAT	Catalase
ChAT	Choline acetyl transferase
ChE	Cholinesterase
CNN	Convolutional neural network
CNS	Central nervous system
CT	Computed tomography
DNP	Donepezil
EAAT2	Excitatory amino acid transporter 2
EC	Enzyme classification
FN	False negative
FP	False positive
GAFF	Generalised amber force field
GSK3	Glycogen synthase kinase-3
iGluRs	ligand-gated ionotropic glutamate receptors
JNK3	c-Jun N-terminal kinase 3
KNN	K-nearest neighbors
LBDD	Ligand based drug design
LDA	Linear discriminant analysis
LGA	Lamarckian Genetic Algorithm
LR	Logistic regression
MACCS	Molecular access system
MD	Molecular dynamics
MEKK	Mitogen-activated Protein/ERK Kinase Kinases
ML	Machine learning
MLP	Multi-layer perceptron
MRI	Magnetic resonance imaging
MSME	Mini-Mental state exam
Nct	Nicastrin
NFT	Neurofibrillary tangle
NMDA	N-methyl D-aspartate
PAC	Passive-aggressive classifier

PAINS	Pan-assay interference compounds
PAM	Positive allosteric modulator
PAMPA	Parallel artificial membrane assay
PAS	Peripheral anionic site
PBL	Porcine brain lipid
PLIP	Protein ligand interaction profiler
PS1	Presenilin 1
PS2	Presenilin 2
QDA	quadratic discriminant analysis
QSAR	Quantitative structure-activity relationship
R_f	Retention factor
RF	Random forest
Rg	Radius of gyration
RMSD	Root mean square deviation
RMSF	Root mean square fluctuation
RO5	Lipinski rule of five
ROC	Receiver operation characteristic
ROS	Reactive oxygen species
RT	Room Temperature
SAR	Structure activity relationship
SASA	Solvent accessible surface area
SBDD	Structure-based drug design
SBVS	Structure based virtual screening
SCO	Scopolamine hydrobromide
SEM	Standard error of mean
SF	Scoring function
SOD	Superoxide dismutase
SVC	Support vector classifier
SVM	Support vector machine
SVR	Support vector regression
TI	Thermodynamic integration
TN	True negative
TP	True positive

Preface

Alzheimer's disease (AD), a progressive neurodegenerative disorder characterized by inexorable cognitive decline and memory impairment, represents a significant and growing public health concern. While existing interventions primarily focused on mitigating cholinergic dysfunction offer symptomatic relief, they fail to address the underlying pathophysiological processes. Recognizing the limitations of current approaches, researchers are delving into the intricate molecular pathways implicated in AD pathogenesis, paving the way for a paradigm shift towards multi-target-directed therapeutic strategies.

C**hapter 1** initiates a comprehensive exploration of AD, encompassing its background, pathophysiology, and the current therapeutic landscape. Additionally, the various methodologies, such as Artificial intelligence (AI), that are involved in drug discovery and design are detailed.

Chapter 2: In this chapter, the objectives of the study and plan of work are mentioned.

Chapter 3: This chapter utilizes machine learning to predict potential BACE-1 inhibitors for AD. By analyzing molecular properties and applying algorithms like SVM and Random Forest, the chapter identifies promising candidates and key structural features associated with BACE-1 inhibition, contributing to the development of targeted AD treatments.

Chapter 4: This section outlines the development and application of an XGBoost-based machine learning model to screen an in-house database for potential BACE-1 inhibitors, a key target in AD treatment. The model utilizes PubChem fingerprints to identify promising candidates, which are then subjected to experimental validation for their inhibition activity.

Chapter 5: This section explores a novel approach for predicting Blood-Brain-Barrier (BBB) permeability of molecules using Natural Language Processing (NLP) and Deep Learning. It utilizes the B3DB database and extracts features from molecules via SELFIES and N-gram tokenization, converting them into numerical vectors. These features are then fed into various Deep Learning models like ANN and LSTM to predict BBB permeability. The best-performing model achieved high accuracy, suggesting its potential for early screening of drugs targeting the central nervous system.

Chapter 6: This section describes developing and evaluating multi-target directed ligands (MTDLs) based on *N-benzylpiperidines* for AD treatment. Utilizing suitable approaches, promising N-benzylpiperidine scaffolds are identified. Synthesis of derivatives with predicted enhanced multi-target activity against BACE-1, cholinesterases, and amyloid aggregation is followed by *in-vitro* and, for promising candidates, *in-vivo* efficacy evaluation in AD animal models.

Chapter 7: This chapter outlines the summary and conclusions of the research work undertaken.

Chapter 8: The references used to carry out the research work are presented in the chapter.

An appendix of additional supporting information, spectral data of representative compounds, and a list of publications from the course of the Ph.D. are included.