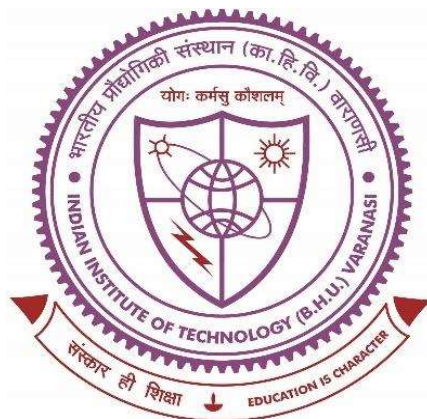


# **Exploring Natural Products and their Semisynthetic Derivatives for the Management of Alzheimer's Disease**



**Thesis submitted in partial fulfillment  
for the Award of Degree  
Doctor of Philosophy**

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It is further certified that the student has fulfilled all the requirements of Comprehensive Examination, Candidacy and SOTA for the award of Ph.D. degree.

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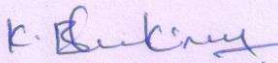
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## List of Abbreviations

### Abbreviations

### Full forms

ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADME	Absorption, Distribution, Metabolism, and Excretion
ATCI	Acetylthiocholine iodide
BBB	Blood-Brain Barrier
BuChE	Butyrylcholinesterase
BTCI	Butyrylthiocholine iodide
CAS	Catalytic active site
CDCl <sub>3</sub>	Deuterated chloroform
DIPEA	Diisopropylethylamine
DMSO	Deuterated dimethyl sulfoxide
DPZ	Donepezil
DPPH	2,2-diphenyl-1-picrylhydrazyl
DTNB	5,5'-dithiobis-2-nitrobenzoic acid
eeAChE	Electric eel acetylcholinesterase
EDC.HCl	1-[3-(dimethylamino)-propyl]-3-ethyl carbodiimide hydrochloride
eqBuChE	Equine butyrylcholinesterase
hAChE	Human acetylcholinesterase
HBA	Hydrogen bond acceptor
HBD	Hydrogen bond donor
HRMS	High-resolution mass spectrometry
HOBT	N-hydroxy benzotriazole
IC <sub>50</sub>	Inhibitory concentration required to kill 50% of the population
MW	Molecular weight

MTT	3- (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium
MTDLs	Multitarget directed ligands
PAS	Peripheral anionic site
TMS	Tetramethyl silane
PDB	Protein data bank
PBL	Porcine brain lipid
Pe	Permeability
RMSD	Root mean square deviation
RMSF	Root mean square fluctuation
SAR	Structural activity relationship
SD	Standard deviation
3D	Three dimensional
TPSA	Topological polar surface area

## List of Symbols

<b>Symbols</b>	<b>Meaning</b>
$\alpha$	Alpha
$\beta$	Beta
$\delta$	Delta
$^{\circ}\text{C}$	Degree Celsius
$\text{\AA}$	Angstrom
mg	Milligram
$\mu\text{g}$	Micro gram
$\mu\text{M}$	Micromole
mmol	Millimole
mL	Milliliter
$\mu\text{L}$	Microliter
h	Hour
s	Singlet
nm	Nanometer
$\mu\text{m}$	Micrometer
mm	Millimeter
cm	Centimeter
ppm	Parts per million
rpm	Revolutions per minute
Kcal	Kilocalories
Hz	Hertz
MHz	Megahertz
J	Coupling constant
d	Doublet
t	Triplet
m	Multiplet

dd	Doublet of doublet
m/z	Mass to charge ratio
%	Percent
pH	Potential of hydrogen
<	Less than
>	More than
±	Plus, or minus

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## Preface

Alzheimer's Disease (AD) is an age-related neurodegenerative disorder, which accounts for more than 80% of dementia cases worldwide in older people. It is characterized by the deposition of A $\beta$  plaque and neurofibrillary tangles. The disease leads to progressive loss of memory, functional ability to learn and is primarily characterized by the progressive loss of memory associated with other cognitive deficits. Despite decades of study on the etiology of disease and also significant efforts by the pharmaceutical industry to develop therapies, there is no effective treatment available to cure AD or inhibit its progression significantly. However, there are few drugs viz. donepezil, galantamine, and rivastigmine, approved by USFDA, acting on cholinergic pathway and memantine acting on NMDA receptor. Recently, Aducanumab and Lecanemab are approved in the US as disease-modifying agents in AD.

Considering the disease complexity and treatment challenges, naturally obtained leads from medicinal plants were selected for drug development. The plant-based drugs like galantamine, physostigmine, and rivastigmine act as cholinesterase inhibitors and are being used to improve memory in AD patients. Several studies are ongoing for the identification of plant-based medications for the management of AD. In this study, natural products and their semisynthetic derivatives were explored as multitarget drug-directed ligands.

The present study is divided into seven chapters:

**Chapter 1** deals with Alzheimer's disease (AD), its pathophysiology, and current treatments for AD.

**Chapter 2** provides insight into the literature reports related to the relevant work.

**Chapter 3** includes the hypothesis, rationale, and plan of the work.

**Chapter 4** bioactivity guided fractionation, characterization, *in vitro*, *in silico*, and *in vivo* studies of *Adhatoda vasica*.

**Chapter 5** design, synthesis, characterization, *in vitro*, *in silico*, and *in vivo* studies of vasicine derivatives.

**Chapter 6** design, synthesis, characterization, *in vitro*, *in silico*, and *in vivo* studies of piperine derivatives.

**Chapter 7** deals with the conclusion and summary

References used to carry out the research work, are presented. An appendix consisting of the additional supporting information, spectral data of representative compounds, and a list of publications during the Ph.D. are included.