

Contents

List of Abbreviations.....	i
List of Symbols	iii
List of Figures.....	v
List of Schemes.....	vii
List of Tables.....	viii
Preface.....	x
1. Introduction.....	1
1.1. Alzheimer's disease	1
1.2. Status of research and development.....	2
1.2.1. International status	2
1.2.2. National status.....	3
1.3. Symptoms	4
1.4. Diagnosis of Alzheimer's disease	4
1.5. Pathophysiology.....	5
1.6. Current clinical drugs for the management of AD	6
2. Literature review.....	9
2.1. Therapeutic role of medicinal plants in Alzheimer's disease	9
2.1.1. Natural products acting through Amyloid hypothesis	11
2.1.2. Natural products acting through Tau hypothesis.....	13
2.1.3. Natural products acting through Ubiquitin–proteasome hypothesis.....	14
2.1.4. Natural products acting through impaired autophagy hypothesis.....	15
2.1.5. Natural products acting through inflammation hypothesis	16
2.1.6. Natural products acting through immune hypothesis	18
2.1.7. Natural products acting through oxidative stress hypothesis.....	20
2.1.8. Natural products acting through mitochondrial cascade hypothesis.....	22
2.1.9. Natural products acting through neurogenesis hypothesis.....	23
2.1.10. Natural products acting through cholinergic hypothesis.....	24
2.2. Contribution of phytoconstituents in the management of Alzheimer's disease	25
2.2.1. Coumarin and curcuminoid derivatives	25
2.2.2. Resveratrol derivatives.....	26
2.2.3. Chromone derivatives	26
2.2.4. Indole derivatives.....	26
2.3. Selection of plant and chemical constituents	27
2.3.1. <i>Adhatoda vasica</i> Nees. (<i>Justicia adhatoda</i> L.)	27
2.3.2. Piperine	31
3. Objective and Plan of work.....	37
3.1. Objective	37
3.2. Plan of work	39
4. Bioactivity-guided isolation of Vasaka	40
4.1. Experimental work	40
4.1.1. Chemicals.....	40
4.1.2. Extraction and Fractionation.....	40

4.1.3. Cholinesterase inhibition assay of vasaka extract and fractions	41
4.1.4. Isolation of active constituents.....	42
4.1.5. Structural characterization of constituents.....	42
4.1.6. Drug-likeness, ADME, and toxicity predictions.....	43
4.1.7. Molecular docking studies	44
4.1.8. Molecular Dynamic simulations	44
4.1.9. Free-radical scavenging assay.....	45
4.1.10. Cholinesterase inhibition assay.....	45
4.1.11. Propidium iodide displacement assay	46
4.1.12. PAMPA-BBB Assay.....	46
4.1.13. A β inhibition activity	47
4.1.14. In vitro neuroprotection assay.....	47
4.1.15. Experimental animals and study design.....	48
4.1.16. Acute oral toxicity.....	48
4.1.17. Scopolamine induced amnesia.....	49
4.1.18. Morris water maze test.....	49
4.1.19. AChE, ACh estimation, and Histopathological studies	51
4.1.20. Statistical analysis.....	52
4.2. Results	52
4.2.1. Chemical and structural properties of isolated compounds	52
4.2.2. Drug-likeness, ADME, and toxicity parameters	53
4.2.3. Molecular docking studies on AChE	54
4.2.4. Molecular docking studies on BuChE	57
4.2.5. Molecular dynamics studies of VAS on AChE	57
4.2.6. Molecular dynamics studies of VA on AChE.....	59
4.2.7. Cholinesterase inhibition activity	60
4.2.8. PAMPA-BBB assay	62
4.2.9. A β aggregation studies.....	62
4.2.10. Propidium iodide displacement assay	63
4.2.11. Neuroprotection studies	64
4.2.12. Acute oral toxicity.....	64
4.2.13. Scopolamine induced amnesia.....	65
4.2.14. A β induced Alzheimer's	66
4.2.15. Histological studies	68
4.3. Conclusion	69
5. Development of vasicine derivatives.....	71
5.1. Experimental section	71
5.1.1. Chemistry	71
5.1.2. In silico studies	83
5.1.3. In vitro studies.....	85
5.1.4. In vivo studies	88
5.2. Results and discussion	93
5.2.1. Extraction and isolation of vasicine	93

5.2.2. Design and synthesis of vasicine derivatives	93
5.2.3. In silico studies	96
5.2.5. In vitro studies.....	103
5.2.6. In vivo studies	110
5.3. Conclusion	118
6. Development of piperine derivatives.....	121
6.1. Experimental section	121
6.1.1. Chemistry	121
6.1.2. In vitro studies.....	136
6.1.3. In silico studies	139
6.1.4. In vivo studies	140
6.1.5. Statistical analysis	143
6.2. Results and discussion	143
6.2.1. Extraction and isolation of piperine	143
6.2.2. Design and synthesis of piperine derivatives.....	143
6.2.3. In vitro studies.....	145
6.2.4. In silico studies	153
6.2.5. In vivo studies	159
6.3. Conclusion	163
7. Summary & Conclusion	164
References	172
Appendices.....	199
HRLCMS chromatogram of DCM extract of Vasaka	199
Supplementary data of vasicinone	200
Supplementary data of vasicine	204
Supplementary data of vasicine derivatives.....	207
Supplementary data of piperine	217
Supplementary data of piperine derivatives.....	220
List of publications.....	231