

Contents

List of Contributors *xv*

Dedication *xix*

Preface *xxi*

Editor Biography *xxv*

1 Neuroprotective Natural Products: Clinical Aspects and Modes of Action – An Overview *1*

Goutam Brahmachari

- 1.1 Introduction *1*
- 1.2 An Overview of the Book *1*
 - 1.2.1 Chapter 2 *1*
 - 1.2.2 Chapter 3 *2*
 - 1.2.3 Chapter 4 *2*
 - 1.2.4 Chapter 5 *3*
 - 1.2.5 Chapter 6 *3*
 - 1.2.6 Chapter 7 *3*
 - 1.2.7 Chapter 8 *4*
 - 1.2.8 Chapter 9 *4*
 - 1.2.9 Chapter 10 *4*
 - 1.2.10 Chapter 11 *5*
 - 1.2.11 Chapter 12 *5*
 - 1.2.12 Chapter 13 *5*
- 1.3 Concluding Remarks *6*

2 Neuroprotective Agents: An Overview on the General Modes of Action *7*

Christina Volsko and Ranjan Dutta

- 2.1 Introduction *7*
- 2.2 Neuroprotective Agents *7*
 - 2.2.1 Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) *7*
 - 2.2.2 Hepatocyte Growth Factor (HGF) *8*
 - 2.2.3 Trophic Factors *9*
 - 2.2.4 Apolipoprotein E (apoE)–Containing Lipoproteins *9*
 - 2.2.5 Prothymosin α (PTMA) *10*
 - 2.2.6 Erythropoietin (EPO) *11*

2.2.7	Neuregulin-1 (NRG1)	11
2.3	Neurodegenerative Diseases	12
2.4	Neuroprotection in Common Neurodegenerative Diseases	13
2.5	Concluding Remarks	16
	Acknowledgments	17
	Abbreviations	17
	References	17
3	Beneficial Upshots of Naturally Occurring Antioxidant Compounds against Neurological Disorders	23
	<i>Sukanya Saha, Pritam Sadhukhan, and Parames C. Sil</i>	
3.1	Introduction	23
3.2	Oxidative Stress	25
3.2.1	Oxidants and Its Types	25
3.2.2	Oxidants: Its Production, Consumption, and Way to Oxidative Stress	25
3.2.3	Oxidative Stress Affecting Various Organs Leads to Different Diseases	27
3.3	Neurological Disorders	28
3.3.1	ROS and Its Way to Oxidative Stress Results in Neurotoxicity	28
3.3.2	Why Is the Brain Particularly Prone to Oxidative Stress?	29
3.3.3	The Different Types of Neurological Diseases	30
3.3.4	Cognitive Diseases	31
3.3.5	Movement Diseases	32
3.4	Beneficial Effects of Different Antioxidants against Various Neurological Disorders	34
3.4.1	Role of Natural Antioxidants in the Amelioration of Different Cognitive Disorders	36
3.4.2	Role of Natural Antioxidants in the Amelioration of Different Movement Disorders	38
3.5	Concluding Remarks	40
	Abbreviations	41
	References	42
4	Natural Neuroprotectives for the Management of Parkinson's Disease	57
	<i>Bharti Gaba, Shobhit Kumar, Shadab Md, Sanjula Baboota, Jasjeet. K. Narang, and Javed Ali</i>	
4.1	Introduction	57
4.2	Role of Antioxidants/Natural Neuroprotectives in PD	58
4.2.1	Vitamin E (α -Tocopherol)	59
4.2.1.1	Animal Studies with Vitamin E	60
4.2.1.2	Human Studies with Vitamin E	61
4.2.2	Naringenin	62
4.2.2.1	Animal Studies with Naringenin	63
4.2.3	Curcumin	64
4.2.3.1	Animal Studies with Curcumin	65

4.2.4	Resveratrol	66
4.2.4.1	Animal Studies with Resveratrol	67
4.2.5	Coenzyme Q10	68
4.2.5.1	Animal Studies with Coenzyme Q10	69
4.2.5.2	Human Studies with Coenzyme Q10	69
4.2.6	Vitamin C	70
4.2.6.1	<i>In Vitro</i> Studies with Vitamin C	71
4.2.6.2	Animal Studies with Vitamin C	71
4.2.6.3	Human Studies with Vitamin C	71
4.2.7	Melatonin	72
4.2.7.1	Animal Studies with Melatonin	73
4.3	Concluding Remarks	74
	Abbreviations	75
	References	75
5	Neuroprotective Effect of Ayurvedic Preparations and Natural Products on Parkinson's Disease	91
	<i>Anupom Borah, Amarendranath Choudhury, Rajib Paul, Muhammed K. Mazumder, and Swapnali Chetia</i>	
5.1	Introduction	91
5.1.1	Therapy for Parkinson's Disease	91
5.2	Parkinsonian Symptoms and Ayurveda	92
5.2.1	Equivalent Parkinsonian Symptoms in Ayurveda	92
5.2.2	Treating Parkinsonian Symptoms with Ayurvedic Preparations	93
5.3	Medicinal Plants in the Ayurvedic Formulation for Parkinson's Disease Therapy	94
5.3.1	Mechanism of Action of Ayurvedic Preparation in PD	96
5.3.1.1	<i>Mucuna pruriens</i>	96
5.3.1.2	<i>Hyoscyamus niger</i>	96
5.3.1.3	<i>Withania somnifera</i>	96
5.3.1.4	<i>Sida cordifolia</i>	97
5.4	Concluding Remarks	97
	Abbreviations	97
	References	98
6	Lipid Peroxidation and Mitochondrial Dysfunction in Alzheimer's and Parkinson's Diseases: Role of Natural Products as Cytoprotective Agents	107
	<i>Carlos Fernández-Moriano, Elena González-Burgos, and Maria Pilar Gómez-Serranillos</i>	
6.1	Introduction	107
6.1.1	Oxidative Stress	107
6.1.2	Lipid Peroxidation	111
6.1.3	Mitochondrial Dysfunction	114
6.1.4	Lipid Peroxidation and Mitochondrial Dysfunction in PD	115
6.1.4.1	Lipid Peroxidation	116
6.1.4.2	Mitochondrial Dysfunction	116

6.1.5	Lipid Peroxidation and Mitochondrial Dysfunction in AD	116
6.1.5.1	Lipid Peroxidation	117
6.1.5.2	Mitochondrial Dysfunction	117
6.2	History and Context	117
6.3	Potential Therapeutic Agents with Natural Origin: Current Knowledge on the Discovery of Newer Drugs	119
6.3.1	Flavonoids	119
6.3.2	Vitamins	121
6.3.3	Carotenoids	123
6.3.4	Alkaloids	125
6.3.5	Non-flavonoid Phenolic Compounds	126
6.3.6	Terpenes	129
6.3.7	Other Compounds	130
6.3.8	Plant Extracts	132
6.4	Future Trends in Research	132
6.5	Concluding Remarks	133
	Abbreviations	134
	References	135
7	Marine-Derived Anti-Alzheimer's Agents of Promise	153
	<i>Kapil Dev and Rakesh Maurya</i>	
7.1	Introduction	153
7.2	Identification of Potent Anti-Alzheimer's Agents from Marine Sources	154
7.2.1	Cholinergic Hypothesis in Treatment of Alzheimer's Disease	154
7.2.1.1	Cholinesterase Inhibitors	154
7.2.1.2	Nicotinic Acetylcholine Receptor Agonists	160
7.2.2	Amyloid Cascade Hypothesis in the Treatment of Alzheimer's Disease	161
7.2.2.1	Secretase Inhibitors	161
7.2.2.2	Anti-aggregation and Clearance Promoters	166
7.2.3	Kinase Modulators in the Treatment of Alzheimer's Disease (<i>Tau</i> Hypothesis)	167
7.2.4	Antioxidant Natural Products	171
7.3	Molecules in Clinical Trials for Alzheimer's Disease from Marine Sources	171
7.4	Concluding Remarks	172
	Acknowledgments	172
	Abbreviations	172
	References	173
8	Natural Products against Huntington's Disease (HD): Implications of Neurotoxic Animal Models and Transgenics in Preclinical Studies	185
	<i>Abhijit Dey</i>	
8.1	Introduction	185
8.2	Methodology	186

8.3	Neurotoxic <i>In Vitro</i> and <i>In Vivo</i> Anti-HD Models	188
8.3.1	Excitotoxic Lesion Models	194
8.3.1.1	Kainic Acid	194
8.3.1.2	Quinolinic Acid	195
8.3.2	Metabolic Toxin Models	195
8.3.3	3-Nitropropionic Acid	196
8.3.4	Transgenic Mouse Models	197
8.3.4.1	Knock-In and Knockout Mouse Models	198
8.3.4.2	Virus-Mediated Mutated polyQ Tracts and mHtt Models	198
8.3.4.3	Transgenic Primate Models	198
8.3.5	Fly (<i>Drosophila</i>) Models	199
8.3.6	<i>Caenorhabditis elegans</i> Model	199
8.3.7	Yeast HD Models	200
8.3.8	Cellular Models of HD	200
8.4	Anti-HD Natural Products and Implications of HD Models	200
8.4.1	Anti-HD Properties of Medicinal Plants	200
8.4.1.1	<i>Bacopa monnieri</i> (L.) Wettst. (Plantaginaceae)	200
8.4.1.2	<i>Boerhaavia diffusa</i> L. (Nyctaginaceae)	201
8.4.1.3	<i>Calendula officinalis</i> L. (Asteraceae)	201
8.4.1.4	<i>Cannabis sativa</i> L. (Cannabaceae)	201
8.4.1.5	<i>Centella asiatica</i> (L.) Urb. (Apiaceae)	202
8.4.1.6	<i>Convolvulus pluricaulis</i> Choisy (Convolvulaceae)	202
8.4.1.7	<i>Garcinia kola</i> Heckel (Clusiaceae)	203
8.4.1.8	<i>Gastrodia elata</i> Blume (Orchidaceae)	203
8.4.1.9	<i>Ginkgo biloba</i> L. (Ginkgoaceae)	203
8.4.1.10	<i>Luehea divaricata</i> Mart. (Malvaceae)	204
8.4.1.11	<i>Olea europaea</i> L. (Oleaceae)	204
8.4.1.12	<i>Panax ginseng</i> C.A. Mey. and <i>Panax quinquefolius</i> L. (Araliaceae)	204
8.4.1.13	<i>Psoralea corylifolia</i> L. (Fabaceae)	204
8.4.1.14	<i>Punica granatum</i> L. (Lythraceae)	205
8.4.1.15	<i>Valeriana officinalis</i> L. (Caprifoliaceae)	205
8.4.1.16	<i>Withania somnifera</i> L. (Dunal) (Solanaceae)	205
8.4.2	Anti-HD Activity of Phytochemicals	205
8.4.2.1	α -Mangostin	205
8.4.2.2	Astragalin	206
8.4.2.3	Berberine	206
8.4.2.4	Celastrol	206
8.4.2.5	Curcumin	206
8.4.2.6	(-)-Epigallocatechin-gallate	206
8.4.2.7	Ferulic Acid	207
8.4.2.8	Fisetin	207
8.4.2.9	Galantamine	207
8.4.2.10	Genistein	207
8.4.2.11	Ginsenosides	207
8.4.2.12	Hesperidin	207
8.4.2.13	Kaempferol	208

8.4.2.14	L-Theanine	208
8.4.2.15	Lutein	208
8.4.2.16	Lycopene	208
8.4.2.17	Melatonin	208
8.4.2.18	Naringin	209
8.4.2.19	Nicotine	209
8.4.2.20	Onjisaponin B	209
8.4.2.21	Protopanaxatriol	209
8.4.2.22	Puerarin	209
8.4.2.23	Quercetin	210
8.4.2.24	Resveratrol	210
8.4.2.25	S-Allylcysteine	210
8.4.2.26	(-)-Schisandrin B	210
8.4.2.27	Sesamol	210
8.4.2.28	Spermidine	210
8.4.2.29	Sulforaphane	211
8.4.2.30	Trehalose	211
8.4.2.31	Vanillin	211
8.4.3	Herbal Formulations with Anti-HD Properties	211
8.5	Synergism: A Novel Approach against Neurological Disorders	212
8.6	Discussion	213
8.7	Concluding Remarks	215
	Abbreviations	215
	References	218

9 Possible Role of Neuroprotectants and Natural Products in Epilepsy:

	Clinical Aspects and Mode of Action	247
	<i>Anil Kumar, Manveen Bhardwaj, and Harshpreet Kaur</i>	
9.1	Introduction	247
9.2	Global Prevalence of Natural Products in Epilepsy	248
9.3	Pathophysiology of Epilepsy	248
9.3.1	Oxidative Stress	249
9.3.2	Mitochondrial Electron Transport Chain	249
9.3.3	Brain Inflammatory Pathways	249
9.3.4	Apoptosis	250
9.4	Role of Neurotransmitters in Neuronal Excitation	250
9.4.1	γ -Aminobutyric Acid (GABA)	250
9.4.2	Glutamate	251
9.4.3	Serotonin	252
9.4.4	Acetylcholine (ACh)	252
9.5	Role of Neuroprotectants in Seizures	252
9.5.1	Alkaloids	253
9.5.2	Flavonoids	254
9.5.3	Terpenoids	254
9.5.4	Saponins	255
9.5.5	Coumarins	255
9.5.6	Antioxidants	255

9.6	Natural Plants against Epilepsy	256
9.6.1	<i>Nardostachys jatamansi</i> (Jatamansi)	256
9.6.2	<i>Cotyledon orbiculata</i> (Seredile, Plakkie, Imphewula)	256
9.6.3	<i>Laurus nobilis</i>	256
9.6.4	<i>Bacopa monnieri</i> (Brahmi)	256
9.6.5	<i>Rhizoma pinelliae</i>	257
9.6.6	<i>Taxus wallichiana</i> (Himalayan Yew)	257
9.6.7	<i>Sutherlandia frutescens</i> (Umwele, Cancerbush)	257
9.6.8	<i>Ficus platyphylla</i> (Dell-Holl)	257
9.6.9	<i>Scutellaria baicalensis</i> (Skullcaps)	257
9.6.10	<i>Harpagophytum procumbens</i> (Devil's Claw)	258
9.6.11	<i>Delphinium denudatum</i> (Jadwar)	258
9.6.12	<i>Withania somnifera</i> (Ashwagandha):	258
9.6.13	<i>Magnolia grandiflora</i> (Him-Champa):	258
9.7	Natural Plants Examined in Epilepsy	259
9.7.1	Capsaicin	259
9.7.2	Curcumin	259
9.7.3	Piperine	259
9.7.4	Quercetin	260
9.7.5	Cod Liver Oil	260
9.7.6	Vitamin C	260
9.7.7	Lycopene	261
9.7.8	Coenzyme Q10	261
9.7.9	Resveratrol	261
9.8	German Herbs in Epilepsy	262
9.9	Complement and Alternative Medicine	263
9.9.1	Psychological Therapies and Mind–Body Techniques	263
9.9.2	Homeopathy	263
9.9.3	Acupuncture	263
9.10	Marketed Formulation of Natural Products in India	264
9.11	Herbs That Induce Seizures	264
9.12	Interaction of Natural Products with Antiepileptic Drugs (AEDs)	264
9.13	Concluding Remarks	267
	References	268
10	Neuroprotective Effects of Flavonoids in Epilepsy	279
	<i>Hossein Hosseinzadeh and Marjan Nassiri-Asl</i>	
10.1	Introduction	279
10.2	Natural Flavonoids with Antiepileptic Potential	281
10.2.1	Rutin	281
10.2.2	Quercetin	281
10.2.3	Vitexin	281
10.2.4	Hesperidin	284
10.2.5	Apigenin	284
10.2.6	Oroxylin A	284
10.2.7	Wogonin	284
10.2.8	Baicalein	284

10.2.9	Luteolin	285
10.2.10	Hispidulin	285
10.2.11	Naringin	285
10.3	Discovery and Development of Newer Agents	285
10.4	Concluding Remarks	286
	Abbreviations	286
	References	287
11	The Role of Noncompetitive Antagonists of the <i>N</i>-Methyl-D-aspartate (NMDA) Receptors in Treatment-Resistant Depression	293
	<i>Gianluca Serafini, Shawn Hayley, Mehdi Ghasemi, and Mario Amore</i>	
11.1	Introduction	293
11.2	Noncompetitive Antagonists of the NMDA Receptors: Ketamine and Its Mechanism of Action	294
11.2.1	The Antidepressant Efficacy of Ketamine	295
11.2.2	Safety and Tolerability of Ketamine	296
11.3	Other Noncompetitive NMDA Antagonists: Selective GluN2B Subunit NMDA Antagonists	297
11.4	Other Noncompetitive NMDA Antagonists: Glycine Binding Site Modulators	298
11.5	AMPA Receptor Activation: A Possible Adjunctive Antidepressant Role?	299
11.6	Discussion and Future Directions	300
11.7	Concluding Remarks	301
	Abbreviations	302
	References	302
12	Safety and Efficacy of Ashwagandha (<i>Withania somnifera</i>)	313
	<i>Shri K. Mishra, Bharathi A. Venkatachalapathy, and Hadi M. Khanli</i>	
12.1	Introduction	313
12.2	Ashwagandha	314
12.2.1	The Plant	314
12.2.2	Safety and Toxicological Evaluation of <i>Withania somnifera</i>	315
12.2.3	Effects of Ashwagandha on Muscle Sarcopenia	316
12.3	Discussion	317
12.4	Concluding Remarks	317
	Abbreviations	318
	References	318
13	Cannabinoids: A Group of Promising Neuroprotective Agents	321
	<i>Laura R. Caltana and Alicia Brusco</i>	
13.1	Introduction	321
13.1.1	The History of Marijuana	321
13.1.2	Current Context	322
13.2	The Cannabinoid System	322
13.3	Cannabinoids and Neuroprotection	325
13.3.1	Cannabinoids in Hypoxia/Ischemia	325

13.3.2	Cannabinoids in Parkinson's Disease	326
13.3.3	Cannabinoids in Alzheimer's Disease	327
13.3.4	Cannabinoids in Epilepsy	327
13.3.5	Cannabinoids in Multiple Sclerosis	328
13.3.6	Cannabinoids in Psychiatric Disorders	328
13.3.7	Cannabinoids in Retinal Diseases	329
13.4	Concluding Remarks	329
	Abbreviations	330
	References	330
	Index	341