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

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1.1 Introduction

The book titled *Neuroprotective Natural Products: Clinical Aspects and Modes of Action* is an endeavor to the present cutting-edge research in the neuroprotective natural products and helps the reader understand how natural product research continues to make significant contributions in the discovery and development of new medicinal entities. The reference is meant for phytochemists, synthetic chemists, combinatorial chemists, biologists, pharmacologists, clinicians, as well as other practitioners and advanced students in related fields. This book, comprising 12 technical chapters, highlights the clinical aspects and modes of action of potential neuroprotective natural products with an intention to unravel their pharmaceutical applicability in modern drug discovery processes in the field of neurodegenerative diseases.

This introductory chapter presents an overview of the book and summarizes the contents and subject matter of each chapter so as to offer certain glimpses of the coverage of discussion to the readers before they go for detailed study.

1.2 An Overview of the Book

This book contains a total of 12 technical chapters – Chapters 2–13; this section summarizes the contents and subject matter of each of these chapters.

1.2.1 Chapter 2

In Chapter 2, Volsko and Dutta have offered an overview on the general modes of action of neuroprotective agents in several neurodegenerative disorders as studied in various animal models. The results suggest that administration of such therapeutic candidates postpones disease progression and increases survival rate. Neuroprotective agents act through certain key pathways associated with

development, maturation, and repair in abnormal pathological environments during neurodegenerative diseases, thereby resulting in the reduction of cellular distress and slowing disease development in the nervous system. Specific trophic factors, polypeptides, and heterodimers activate or block the receptors during pathogenesis to slow disease progression. Natural neuroprotective agents that are effective in humans and suppress symptoms and delay disease progression are regarded as promising lead candidates in the drug discovery process in treating neurodegenerative diseases. Modifying treatments based on neuropathology of each such disease is essential, and this chapter boosts the ongoing research in this remarkable field.

1.2.2 Chapter 3

Sil and his group have furnished a thorough discussion on the beneficial effects of different classes of naturally occurring antioxidant compounds against various neurological disorders in Chapter 3. Oxidative stress (elevation of intracellular reactive oxygen species level) is a major cause in the development and progression of neurological diseases such as neurodegenerative diseases, movement disorders, and so on. The brain in particular is prone to this oxidative stress phenomenon, and impairment in memory and cognition are hallmarks of progressive neurodegenerative diseases. Therefore, targeting these diseases with antioxidants may be expected to be a fruitful solution. Antioxidant molecules combat oxidative stress by neutralizing excessively produced free radicals and inhibiting them from initiating the signaling cascades and chain reactions that result in various diseases and premature aging. Several natural compounds with antioxidant property have been found to be greatly effective in treating these diseases as they effectively scavenged free radicals and inhibited their generation. This chapter covers the sources of such antioxidants and the general mechanism by which they play a protective role in different cognitive and movement-related neurological disorders. This illuminating review on natural antioxidants would obviously enrich the readers and would motivate them in undertaking in-depth further research.

1.2.3 Chapter 4

Chapter 4 is dedicated to natural neuroprotectives for the management of Parkinson's disease (PD) by Ali and his group. PD is regarded as the second most general neurodegenerative disorder that involves a decreased nigrostriatal availability of dopamine, resulting in motor impairment including bradykinesia, rigidity, and tremor. Currently, the exact cause of this devastating disease is unclear with no single factor accountable for neurodegeneration. It shows that several factors may contribute to its development, such as formation of reactive oxygen species (ROS), protein misfolding, and neuroinflammation. The deficiency of dopamine occurs due to loss of dopaminergic neurons and degradation of dopamine. It has been evidenced that oxidative stress is critically involved in the pathogenesis of PD, and thus antioxidants may find beneficial role in treating the disease. This chapter deals with the literature covering the use of various natural antioxidative neuroprotective agents including naringenin, curcumin,

vitamin E, vitamin C, resveratrol, coenzyme Q10, and melatonin, which may find application in PD. In addition, the authors have discussed on the mechanism of actions and *in vitro* and *in vivo* application of natural neuroprotectives in experimental animal models and in patients with PD. This chapter offers an up-to-date development in this field.

1.2.4 Chapter 5

In Chapter 5, Borah and his group have discussed the role and therapeutic efficacy of Ayurvedic preparations in treating Parkinson's disease (PD). A prospective clinical trial on the effectiveness of an Ayurvedic formulation, composed of *Mucuna pruriens*, *Withania somnifera*, *Hyoscyamus niger*, and *Sida cordifolia*, on PD patients demonstrated significant improvement of the symptoms. The authors have elaborated the potentials of such natural products used in Ayurvedic formulations as alternative/adjuvant to the dopamine replenishment therapy for PD and also highlighted their molecular mechanisms of action.

1.2.5 Chapter 6

Chapter 6 deals with the role of natural products as cytoprotective agents against lipid peroxidation and mitochondrial dysfunction in Alzheimer's and Parkinson's diseases by Gómez-Serranillos and her group. Among their pathological hallmarks, increased lipid peroxidation and mitochondrial dysfunction appear to be relevant from the early events of these age-related disorders. Neurodegenerative diseases in humans are strongly associated with oxidative stress generated by ROS, which can cause oxidative damage to cell structures, including alterations in membrane lipids, proteins, and DNA. In turn, it may trigger cellular organelle dysfunction that finally leads to cell death. Lipid peroxidation is a process that takes place along the cell membrane by effect of free radical oxidation of polyunsaturated fatty acids, and as a consequence of this chain reaction, it results in the formation of reactive products with toxic effects. Mitochondria are cytoplasmic organelles that regulate both metabolic and apoptotic signaling pathways, including energy generation; thus, they exhibit special susceptibility to oxidative stress, which eventually provokes the mitochondrial dysregulation. Herein, the authors have provided a detailed overview of the involvement of lipid peroxidation and mitochondrial dysfunction in Parkinson's and Alzheimer's diseases, with special consideration to natural products exerting beneficial effects on neurodegeneration models through an amelioration of these molecular disorders.

1.2.6 Chapter 7

Dev and Maurya have presented an exhaustive review on potential marine-derived anti-Alzheimer's agents in Chapter 7. Marine secondary metabolites develop under very adverse conditions and, thus, may contain very unusual structural skeletons; such chemical entities with new and varying scaffolds and interesting biological activity have created a new hope of drug discovery and development for various disease areas including neurodegenerative disorders. The main hurdle in drug discovery for Alzheimer's disease is associated with the

permeability of blood–brain barrier (BBB) to exhibit drug's effective activity. A number of marine natural products and their synthetic analogs showed efficacy with good bioavailability against Alzheimer's disease. This chapter includes 163 compounds and some extracts from different marine sources such as algae, sponges, coelenterates, bryozoans, molluscs, tunicates, and echinoderms together with their pharmacological activity in the treatment of Alzheimer's disease. This informative review would act as a stimulus in this direction.

1.2.7 Chapter 8

Huntington's disease (HD) is a neurological disorder characterized by abnormal body movements (chorea) associated with cognitive and motor dysfunctions, neuropsychiatric disturbances, and striatal damage. Therapeutic advancement in screening of natural products against HD suffers from constraints such as limited animal models and giving maximum emphasis on cellular models during experimentations. However, recent progress in animal HD transgenic models expressing mutant proteins may reveal the therapeutic efficacy of natural products against HD, a disease with less elucidated pathogenesis and inadequate treatment strategies. In Chapter 8, Dey has offered an illuminating and comprehensive account on the anti-HD efficacy of a number of plant extracts, fractions, and isolated compounds investigated in various neurotoxic animal models and transgenics highlighting their ability to influence signaling pathways, leading to neuromodulation and probable neuroprotection.

1.2.8 Chapter 9

Chapter 9 by Kumar and his group deals with the possible role of neuroprotectants and natural products in epilepsy, a common neurological problem with complex pathology and uncured treatment. The roles of oxidative stress, mitochondrial dysfunction, and neuroinflammation have been well suggested to explain its pathophysiology and related complications, particularly cognitive dysfunction. Several antiepileptic drugs have been in use for the treatment and management of epilepsy, but majority of them are often associated with the problems due to either side effects, drug interactions, or treatment resistance. Different neuroprotectants of diverse nature are being tried with limited success. In search of new and more efficacious drugs, researchers have been engaged to explore therapeutic potentials of plant-based bioactive molecules, particularly belonging to the alkaloid, flavonoid, terpenoid, saponin, and coumarin skeletons, which have been found responsible for their anticonvulsants properties. In this chapter, the authors have made a significant attempt to highlight the potential role of various natural neuroprotectants, their modes of action, and clinical aspects/status for the treatment of epilepsy and related problems.

1.2.9 Chapter 10

Hosseinzadeh and Nassiri-Asl have presented an account on the neuroprotective effects of flavonoids in epilepsy in Chapter 10. Flavonoids are present in foods such as fruits and vegetables, and these natural polyphenolics are reported to

possess beneficial effects against many neurological disorders including epilepsy, a serious but common problem in our society. It seems that many of these compounds are ligands for γ-aminobutyric acid type A (GABA-A) receptors in the central nervous system. Furthermore, flavonoids have well-established antioxidants and free radical scavenging activities. The authors have discussed such effects in their presentation.

1.2.10   Chapter 11

Chapter 11 is devoted to the role of noncompetitive antagonists of the N-methyl-D-aspartate (NMDA) receptors in treatment-resistant depression by Serafini and coauthors. The authors have discussed the pros and cons of using NMDA antagonists in treating the disease manifestation. As mentioned, ketamine (an NMDA antagonist) exhibits good response as a useful clinical agent in cases of severe intractable depression and suicidal risk; the drug works rapidly in many such patients but is not devoid of adverse effects. Hence, it is of critical importance to develop alternate NMDA or other novel antidepressants as well as possible combinatorial drug approaches to treat depression. For instance, novel agents that target AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors are currently being explored; it has been found that compounds able to exert neurotrophic effects and anti-inflammatory drugs might be useful as add-on (or adjuvants) with traditional antidepressants. The authors are in opinion that more personalized approaches will be the way of the future.

1.2.11   Chapter 12

Mishra and coauthors have presented an overview of the safety and efficacy of Ashwagandha (*Withania somnifera*), an important medicinal plant used in Ayurvedic preparations to treat various diseases including neurological disorders, in Chapter 12. Medicinal herbs in Ayurveda have been widely used for thousands of years to promote health and treat diseases. However, limited evidence is available to testify the safety and efficacy of Ayurvedic herbs. An integrated approach for safety assessment focused on the hazard identification is imperative. Under this purview, this chapter highlighting the safety and efficacy of Ashwagandha plant is of interest.

1.2.12   Chapter 13

Chapter 13 deals with the neuroprotective properties of cannabinoids by Laura and Alicia. The cannabinoid system is well characterized, and abundant research supports their role in ameliorating neuropathologies such as ischemia, Alzheimer's diseases (AD), Parkinson's disease (PD), multiple sclerosis, retinal diseases, and psychiatric disorders. Hence, the manipulation of the endocannabinoid system, using phytocannabinoids or synthetic cannabinoids, could lighten the processing in the treatment and evolution of cerebral diseases. Certain clinical trials have also demonstrated promising results; however, cannabinoid adverse effects still remain to be elucidated. The authors have discussed all such considerations in this chapter.

1.3 Concluding Remarks

This introductory chapter summarizes each technical chapter of the book for which representation of facts and their discussions are exhaustive, authoritative, and deeply informative. The readers would find interest in each of the chapters, which practically cover a wide area of neuroprotective natural product research, particularly on their clinical aspects and modes of action. The reference encourages interdisciplinary works among chemists, pharmacologists, clinicians, biologists, botanists, and agronomists with an interest in these bioactive natural products. Hence, this book would surely serve as a key reference for recent developments in the frontier research on neuroprotective natural products and also would find much utility to the scientists working in this area.