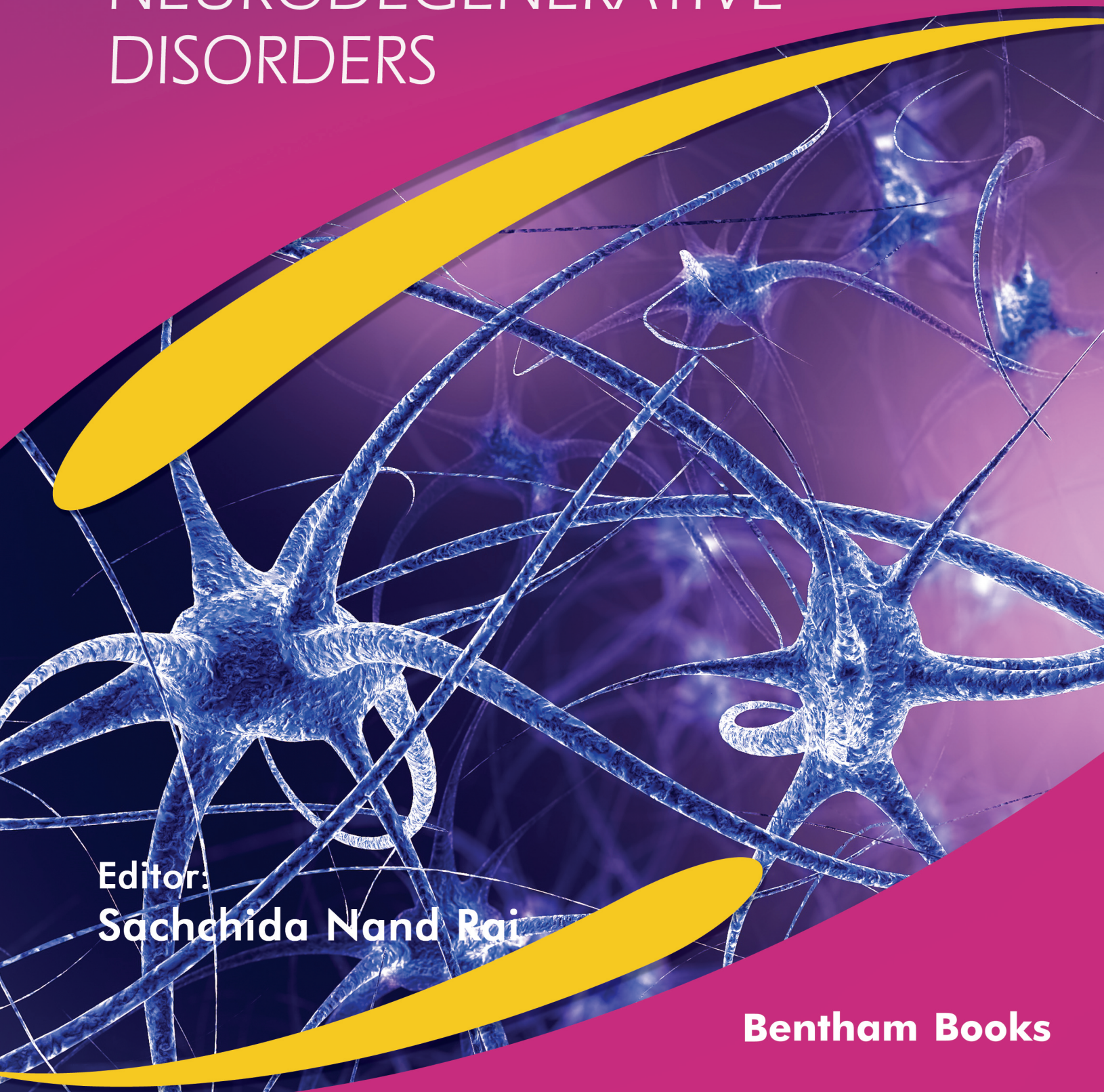
RECENT ADVANCES IN THE TREATMENT OF NEURODEGENERATIVE DISORDERS



Editor:
Sachchida Nand Rai

Bentham Books

Recent Advances in the Treatment of Neurodegenerative Disorders

Edited by

Sachchida Nand Rai
Centre of Biotechnology
University of Allahabad
India

Recent Advances in the Treatment of Neurodegenerative Disorders

Editor: Sachchida Nand Rai

ISBN (Online): 978-1-68108-772-6

ISBN (Print): 978-1-68108-773-3

ISBN (Paperback): 978-1-68108-774-0

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Ltd.
Executive Suite Y - 2
PO Box 7917, Saif Zone
Sharjah, U.A.E.
Email: subscriptions@benthamscience.net

CONTENTS

FOREWORD

A limited boom in neurodegenerative diseases (NDDs) and their treatments attract scientists all around the world. However, the conventional medications of NDDS are not sufficient to provide a better cure for patients. Surgical alternatives also have minimal efficacy with different kinds of side effects. Likewise, advancement in alternative treatment for different NDDs is essential nowadays. Chemically mediated therapy also have a minimal impact, which is associated with significant side-effects. The blood-brain barrier is the biggest culprit to minimize the response of different drugs. Nanoparticles and nanoformulation-based treatment can overcome the BBB problem and improve the efficacy of treatments. Therefore, eating habit also has a significant impact on the management of NDDs. The herbs and plant extracts serve as a better alternative with minimal side-effects. However, edible mushrooms can treat various kinds of NDDs, like Parkinson's disease (PD) and Alzheimer's (AD).The gut biome modulates the therapeutic efficacy in most common NDDs like PD and AD. Polyphenols also show the maximum impact on the treatment of NDDs. Moreover, animal models play a vital role in the standardization of drugs for the treatment of NDDs. Different yoga postures and techniques have a beneficial impact on the management of different neuronal diseases. As mentioned earlier, these options are the most advanced alternatives for treating diverse kinds of brain disorders. In this book, the editor has included all the above-mentioned recent advancements for the medication of neurological disorders. This book attracts the interest of researchers and scientists to explore the current treatment option in their researches. It draws both basic and clinical kinds of research to utilize a different alternative option that will be very efficient in treating NDDs. The literature in this book will be significantly crucial for the academicians, molecular biologists, graduates, and undergraduate students engaged in basic and clinical research. The mentioned distinct tools and techniques in this book can unravel the problem of different NDDs. However, we believed that the information that will be gainedby reading the chapters includedin this book, edited by Dr. Sachchida Nand Rai. The later exchange on every topic serves as an essential and valuable tool to understand the different and more advanced alternative treatment options for different Neurological disorders.

Emanuel Vamanu
University of Agricultural Sciences and
Veterinary Medicine
Bucharest
Romania

PREFACE

The central nervous system (CNS) is the most vital component of our body, regulating various kinds of daily activities that are essential for our life processes. Keeping the balance between body and brain and maintaining the homeostasis of CNS is one of the main focuses of researchers nowadays.

Neurodegenerative diseases (NDDs) arise as a result of progressive degeneration of neurons in the CNS. Researchers have tried various effective treatments that prevent this progressive neurodegeneration of neurons within the CNS. Parkinson's disease (PD), Alzheimer's disease (AD), Multiple sclerosis (MS), *etc.,*are some of the most common NDDs. Conventional treatment has limited success in the treatment of NDDs. The primary aim of this book is to provide an audience worldwide with recent advancements in treating various kinds of Neurological disorders.

This book comprises a new efficient treatment strategy for different kinds of neuronal disorders. It will help in the advancement of alternative treatment scheme for NDDs. In addition, recent nanoparticle-mediated protection for NDDs has also been included in this book. Therefore, the section contains various knowledge that focused on the role of enzyme and polyphenols for PD and AD, respectively.

This book also demonstrates some yoga techniques in the management of NDDs. Moreover, this book explores the natural compound and nanoformulation-based treatment of different NDDs, which are the most advanced treatment options. This book also covers the MS medication strategy by demonstrating the vital effect on animal models. Gut-brain axis based therapy of AD and PD is a hottopic, which is also included in the book chapters. However, Ayurvedic medicine for different NDDs has also been mentioned. Mushrooms mediated treatment of PD and AD is also included for better exploratory knowledge. Thus, we can say that this edition shows distinct advanced treatment alternatives that inevitably attract the interest of scientists and researchers working on NDDs. They can utilize various alternative treatment options for treating neurological disorders. Besides, researchers and scientists all across the world can also use different approaches to the treatment of brain-related ailments disorders. Furthermore, they can also learn separate tools and techniques that have been mentioned in the chapters of the book for NDDs analysis. Thus, it will be a complete package for researchers and scientists working in various fields of NDDs.

Sachchida Nand Rai
Centre of Biotechnology
University of Allahabad
India

ACKNOWLEDGEMENTS

Words are sometimes hard to find when one tries to say thanks for something, as priceless as loving criticism, considerate helpfulness, and valuable guidance. Though facts must be evidently acknowledged, and honest thankfulness must be unequivocally stated. This is what I have humbly attempted to do here.

Above all, I would like to thank the Almighty for making a way and helping me with every step of my life and in the successful completion of this book.

I cannot forget the affection, innumerable blessings, and strength that were bestowed on me by my family. I thank God for giving me wonderful parents Dr. Ravindra Rai and Mrs. Asha Rai, who sincerely raised me with their care and gentle love and have immense faith in me, which brought this work to completion. I would also like to appreciate the support and assistance provided by my uncle and aunty for their consistent love, blessings, and encouragement. I have no words to express my gratitude to my wife Payal Singh, my sister Reena Rai and my brother Ashwini Kumar Rai for their constant support and help during the preparation of this book.

The editor would like to acknowledge UGC Dr. D.S. Kothari Postdoctoral scheme for awarding the fellowship to Dr. Sachchida Nand Rai (Ref. No-F.4-2/2006 (BSR)/BL/19-20/0032).

List of Contributors

Bajaj Priyanka	Institute of Microbial Technology, Sector 39A, Chandigarh- 160036, India
Bajaj Tania	Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab-142001, India
Chaturvedi Abhishek Kumar	Central Government Health Scheme, Ministry of AYUSH, New Delhi, India
Chaturvedi Mridula	Amity Institute of Biotechnology, Amity University, Noida, Uttar Pradesh, India
Dewangan Jayant	Genotoxicity lab, CSIR-Central Drug Research Institute, Lucknow, India
Gautam Priyanka	Department of Neurology, Institute of Medical Sciences,Banaras Hindu University, Varanasi, Uttar Pradesh, India
Gupta Nidhi	Department of Psychology, D.D.U. Gorakhpur University, Gorakhpur-273001, Uttar Pradesh, India
Heer Hemraj	Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab-142001, India
Jamal Farrukh	Department of Biochemistry, Rammanohar Lohia Avadh University, Faizabad, Uttar Pradesh, India
Jogi Mukesh Kumar	Department of Neurology, Institute of Medical Sciences,Banaras Hindu University, Varanasi, Uttar Pradesh, India
Kaur Vishav Prabhjot	Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab-142001, India
Khan Nilofar	Amity Institute of Biotechnology, Amity University, Maharashtra, 410206, India
Kumar Raushan	Department of Biochemistry, University of Allahabad, Allahabad-211002, Uttar Pradesh, India
Kushwaha Ankita	Centre of Biophysics, Ewing Christian College, Prayagraj-211003, India
M.P. Singh	Centre of Biotechnology, University of Allahabad, Prayagraj, India
Pandey Prabhash Kumar	Department of Biochemistry, Faculty of Science, University of Allahabad, Prayagraj, Uttar Pradesh, India
Pathak Abhishek	Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India
Patil Ravishankar	Amity Institute of Biotechnology, Amity University, Maharashtra, 410206, India
Rai Sachchida Nand	Centre of Biotechnology, University of Allahabad, Prayagraj, India
Rath Srikanta Kumar	Genotoxicity lab, CSIR-Central Drug Research Institute, Lucknow, India
Sanjay C. Masih	Department of Zoology, Ewing Christian College, Prayagraj-211003, India
Sarma Jayasri Das	Department of Biological Sciences, Indian Institute of Science Education and Research, Kolkata, Mohanpur, Nadia, West Bengal 741246, India

Sengupta Sourodip	Department of Biological Sciences, Indian Institute of Science Education and Research, Kolkata, Mohanpur, Nadia, West Bengal 741246, India
Singh Abhishek Kumar	Amity Institute of Neuropsychology and Neurosciences, Amity University, Noida-201313, Uttar Pradesh, India
Singh Arti	Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab-142001, India
Singh Charan	Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab-142001, India
Singh Payal	Department of Zoology, MMV, BHU, Varanasi, India
Singh Ranjan	Department of Biotechnology, Choithram College of Professional Studies, Indore, Madhya Pradesh, India
Tripathi Shambhoo Sharan	Department of Biochemistry, University of Allahabad, Prayagraj-211002, Uttar Pradesh, India
Vivek K. Chaturvedi	Centre of Biotechnology, University of Allahabad, Prayagraj-221002, India

CHAPTER 1

An Introduction to Neurodegenerative Diseases and its Treatment

Payal Singh[1] and **Sachchida Nand Rai**[2,*]

[1] *Department of Zoology, MMV, Banaras Hindu University, Varanasi-221005, India*

[2] *Centre of Biotechnology, University of Allahabad, Prayagraj-221002 , India*

Abstract: In the 21st century, a lot of progress has been made in the treatment against different kinds of Neurodegenerative disorders (NDs). Antioxidant therapy is one of the most common types of therapy for NDs. Among Antioxidant therapy, reduced GSH delivery systems are widely utilized. Gut-microbiome based treatment is also widely accepted. The blood-brain barrier (BBB) is one of the major hurdles that reduce the efficacy of several neuroprotective drugs. That is why nanoformulation based drug is currently trending to potentially treat the neurodegenerative disease. 3D organoid model is employed to mimic the *in vivo* condition for the development of drugs for NDs. Target specific surgical interventions are also utilized to improve the symptoms of neurological diseases. Chemical compound mediated protection only provides symptomatic relief. In long term usage, this chemical compound causes several side effects. Herbal plant-mediated therapy is a better alternative for the same. Diet is a basic part of our life. By manipulating our diet in such a way that include several beans may be very helpful in the treatment of several NDs. Accordingly, this chapter explores some important recent advancement in the treatment of different NDs.

Keywords: Alzheimer's disease, Huntington's disease, *Mucuna pruriens*, Parkinson's disease, Ursolic acid.

INTRODUCTION

In recent years, several targets for different neurodegenerative diseases (NDs) have been identified and tested for therapeutic implications. Different areas of the brain have been explored to find a connection between neuroanatomy and disease progression. Sporadic and genetic level factors have been taken into consideration for therapeutic response against these diseases. Ayurveda provides a very efficient way to prevent progressive degeneration in NDs [1]. The gut-brain axis was explored by several researchers to establish a link between the gut and brain [2]. The following are some advancements made in the treatment of NDs.

* **Corresponding author Sachchida Nand Rai:** Centre of Biotechnology, University of Allahabad, Prayagraj-221002 , India; Tel: +91 9616503505; E-mail: raibiochem@gmail.com

AYURVEDA IN NEURODEGENERATIVE DISEASES (NDS)

Ayurveda plays a very important role in the prevention of different NDs. The progression of several NDs as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), and Amyotrophic lateral sclerosis (ALS), has been slow down by different Ayurvedic and herbal plant [3]. The bioactive components present in these Ayurvedic and herbal plants are mainly responsible for the underlying therapeutic responses [4]. In PD, *Mucuna pruriens* (Mp) protected the death of dopaminergic neurons in substantia nigra pars compacta (SNpc) and in the striatum (ST) through NF-κB and pAkt1 pathways [5]. The seed extract of Mp contains a significant amount of levodopa (L-DOPA) that provides the major symptomatic response in PD [5, 6]. Ursolic acid (UA) is the major bioactive components in the seed extract of Mp that also shows potent Anti-Parkinsonian activity in the toxin-induced PD mouse model [7, 8]. Similar to Mp, *Withania somnifera* (Ws) also exhibits strong antioxidative activity in the toxin-induced PD mouse model by targeting the apoptotic pathway [9, 10]. Similar to UA, chlorogenic acid (CA) is also found in several herbal plants that exhibit potent anti-oxidative and anti-inflammatory activity in the PD model by modulating the mitochondrial pathways [11, 12]. *Tinospora cordifolia* (Tc) prevented the progressive neurodegeneration in PD by its antioxidative and anti-inflammatory activity in the toxin model of PD [13]. Inflammation is the common characteristics in almost all NDs. Mp inhibits the inflammation in LPS induced in *vitro* cells and might play an important role in the treatment of all NDs [14]. Mp also exhibits its therapeutic activity in the stroke (ischemia) model of rats [15]. The bioactive components of Ws also show therapeutic activity in AD. Withanamides is vital bioactive constituents of Ws that protect from beta-amyloid-induced toxicity in PC12 model of AD [16]. In silico analysis along with integrated system pharmacology shows the potent therapeutic activity of Ws in AD [17]. Ws also shows its therapeutic potential by inhibiting the production of amyloid beta through neuroinflammatory and epigenetic pathways in the AD *in vitro* model [18]. Withanolide is also an important bioactive component in Ws that exhibits neuroprotective activity *via* the intranasal route in the ischemia model of mice [19]. *Gastrodiaelata* (GE) is also an important herbal plant that controls the morphology of mitochondria by attenuating protein aggregations induced by mutant huntingtin [20]. In the 3-nitropropionic acid-induced HD model, seed extracts of *Psoralea corylifolia* Linn. show a neuroprotective effect by improving mitochondrial dysfunction [21]. In the spinocerebellar ataxia 3 cell model, an aqueous extract of *Glycyrrhiza inflata* inhibits aggregation by upregulating PPARGC1A and NFE2L2-ARE pathways [22]. GE also inhibits the aggregation of huntingtin proteins through the activation of the ubiquitin proteasomal system and adenosine A2A receptor [23].

In this way, we can say that Ayurvedic plants and their bioactive components show promising therapeutic activity in different NDs. Further study will be needed to explore the additional Ayurvedic plants and their bioactive components against NDs.

VITAMINS IN NEURODEGENERATIVE DISEASES (NDS)

In this COVID-19 pandemic, vitamins show a very promising response against the viral load [24]. Clinical trials on COVID-19 patients prove that vitamins fight strongly against coronavirus by enhancing host immunity [25, 26]. The neurological symptoms in COVID-19 patients were well managed by vitamin supplementation [27]. Both water-soluble vitamins and lipid-soluble vitamins exhibit immune-enhancing activity and have been tested against different ND, as shown by several types of research. Vitamin D (VitD) improves the cognitive functions in PD, and its low level may be a potential biomarker of mild cognitive impairment [28]. Similarly, ascorbate also improves the cognitive function in PD and decreasesthe urate concentration [29]. Supplementation of Vitamin B9-B12 improves the cognitive functions by neurogenesis in aged rat models who are subjected to gestational and perinatal deficiency of the same vitamins [30]. Vitamins also modulate the progression of AD through multiple pathways [31]. A deficient level of VitD enhances the AD-like pathologies by reducing the antioxidative potential [32]. Vitamin A (VitA) and retinoic acid also improve the cognitive function in cognitive disease [33]. The receptor of retinoic acid is a very important component in all NDs and might be targeted for vitamin supplementation-based therapy [34].

Thus, vitamin supplementation is very vital to improve our immune function and also to manage the neurological symptoms found in different NDs.

GUT-BRAIN AXIS AND ASSOCIATED PRO AND PRE-BIOTICS THERAPY FOR NDS

The dysfunctional gut-brain axis is found in NDs, and it could be an early sign of the disease condition as like in PD, AD, and HD [35 - 37]. Repeated infection of few pathogens like *Citrobacter rodentium is* responsible for the PD pathology in *Pink1*$^{-/-}$ mice compared to wild type. Characterization of the gut shows the disturbance in the level of short-chain fatty acids and butyric acid in the PD model *versus* control. Thus, gut-brain homeostasis plays a very important role in PD progression [38]. Probiotics and prebiotics treatment prove to beimproved the homeostasis of different NDs by balancing the activity of the gut-brain axis [39]. The gut microbiome modulates various signaling pathways as it balances the epigenetic pathways in NDs [40]. In diet-induced obese mice, cognitive impairment was significantly alleviated by beta-glucan [41]. Gut dysbiosis is

CHAPTER 2

Recent Advancement in the Treatment of Neurodegenerative Diseases by Ayurveda

Mridula Chaturvedi and **Abhishek Kumar Chaturvedi***

Amity Institute of Biotechnology, Amity University, Noida, Uttar Pradesh, India and Central Government Health Scheme, Ministry of AYUSH, New Delhi, India

Abstract: Neurodegenerative diseases (NDDs) are not the only diseases but a key term for a range of conditions that mainly affect the neurons in the human brain resulting in progressive degeneration or death of the nerve cells, which is a deadly and debilitating state. It affects millions of people worldwide. The most common NDDs worldwide are Parkinson's disease (PD) and Alzheimer's disease (AD). According to De Lau & Breteler *et al.*, the incidence of PD is about 10 million globally (*i.e.,* approximately 0.3% of the world population) and 1% of those above 60 years. Management of NDDs has become a big challenge in the modern system of medicine & public health at present because of demographic changes worldwide. There is no specific therapy for the conventional management of NDDs in the modern system of medicine. The absence of specific and complete therapy for NDDs in the present era makes Ayurveda more important to consider some alternative and complementary system of medicine for the treatment. Ayurveda is an Indian system of medicine that comes under AYUSH and treats the NDDs since its inception, which is mainly described under the VataVyadhi (neurological disorder) context. In this chapter, the recent advancement in Ayurvedic medicinal plants, RasaAusadhies (herbo-mineral drugs) & combined drugs, *Panchkarma* therapies (bio-purification procedures), and Yoga & Asanas (bodily postures) that successfully treat the various common NDDs worldwide will be described.

Keywords: Alzheimer's diseases, Ayurveda, Herbo-mineral drugs, Neurodegenerative diseases, *Panchkarma*, Parkinson's disease, Yoga.

INTRODUCTION

The building blocks of the nervous system (brain and spinal cord) are neurons that generally do not replace or reproduce if they become dead or damaged, result in

* **Corresponding author Abhishek Kumar Chaturvedi:** Central Government Health Scheme, Ministry of AYUSH, New Delhi, India; Tel: +91 8743012029; E-mail: abhishek.bhumedical@gmail.com

Sachchida Nand Rai (Ed.)

problems in the movement known as ataxias or mental function known as dementias [1]. Due to this, they are responsible for the greatest trouble of neurodegenerative disorders in which Parkinson's disease (PD) and Alzheimer's disease (AD) contributes approximately 60-70% of cases worldwide [2]. At cellular, molecular as well as subcellular level, most of the neurodegenerative diseases (NDDs) exhibit the common features [3]. In common NDDs, various intracellular and extracellular changes can be observed, especially in Alzheimer's, Parkinson's, Huntington's, and other NDDs [4]. In the living organism, the cytoplasm and reticulum are mainly conscientious for the fabrication of structural and functional protein molecules for which the mechanism of translational and post-translation synthesis is extremely multifaceted and complicated [5]. The main characteristics of NDDs are amassing of anomalous protein aggregation that leads to inflammation as well as oxidative stress (OS) in the central nervous system (CNS) [6]. These NDDs (PD & AD) are caused by environmental and genetic influences [7].

Scientists recognize that the amalgamation of a person's genes and environment contributes to the threat of developing NDDs. That is, a person may have a gene that makes him more vulnerable to certain NDDs. But how severely the person is exaggerated depends on environmental exposures throughout life [8]. NDDs are exemplified by aggregation of proteins, inflammation, and OS in the CNS, degradation of neurotransmitters in the synaptic cleft due to the elevated activity of enzymes, mitochondrial dysfunction, and excitotoxicity of neurons [9]. Deficiency or inadequate synthesis of neurohormones and transmitters, anomalous ubiquitination, and stress are directly related to NDDs and also some other induced origin including the drugs which are used for the treatment of autism, and other chronic illnesses are not without side effects and injure the blood-brain barrier which leads to various nervous system related disorders [10].

OVERVIEW OF NEURODEGENERATIVE DISEASES (NDDS)

The progressive loss of function as well as the structure of neurons due to known cause or unknown cause, including the death of neuronal cells, are called NDDs. Many NNDs are discovered, which are the result of these degenerative process in which PD, AD, and Huntington's disease (HD) are most common [11]. Such diseases are fatal, not curable, and permanent in nature, resulting in a debilitating situation for the patient. As research works progress, many similarities come into view that linkthese diseases to one another on a sub-cellular level [12].

The Preamble of Common Neurodegenerative Diseases

Several NDDs are discovered since the beginning, but the most common accounts of 70% of cases worldwide are preamble and are discussed below:

Alzheimer's Disease (AD)

The main features of this disease are neuronal inflammation, cognitive decline, neuronal loss, and neuronal death, which are also known as apoptosis. The main etiology of AD is an aggregation of *β*-amyloid (A*β*). The formation of microtubule associated protein *i.e.* hyper-phosphorylated Tau in the neurons is directly related to the AD [13].

Parkinson's Disease (PD)

This is an example of movement disorder and is characterized mainly by the abnormal accumulation of α-synuclein protein in the neurons [14].

Huntington's Disease (HD)

This disease is a typical NDDs of the CNS and mainly occurs due to the aggregation of abnormal long polyglutamine [15].

NDDs can be generally classified by their scientific presentations, with extrapyramidal and pyramidal movement disorders and cognitive or behavioral disorders being the most frequent. Few patients have pure syndromes, with most having dissimilar clinical features. Although NDDs are classically defined by specific protein accumulations and anatomic susceptibility, they share many elementary processes associated with progressive neuronal dysfunction and fatality, such as proteotoxic stress and its attendant abnormalities in ubiquitin–proteasomal and autophagosomal/lysosomal systems, OS, programmed cell death, and neuroinflammation (Table **1**) [16].

Table 1. Neurodegenerative diseases, clinical features, and etiology & pathological findings.

S. No.	Common Neuro-degenerative Diseases	Clinical Features	Etiology/Pathological Findings	References
1.	Alzheimer's disease (AD)	Commonest NDDs, loss or decrease in memory, alterations in the frame of mind and activities, a most common and frequent cause of dementia, disorientation, and aphasia	Senile or neuritic plaques and neurofibrillary tangles are the main characteristic lesions in affected tissues. Along neuronal axons, Tau protein is normally involved in nutrient transport and directly linked to AD. In AD, the cerebral cortex and hippocampus lobes are severely affected	[17 - 18]

CHAPTER 3

Role of Phytochemicals in Neurodegenerative Disorders

Shambhoo Sharan Tripathi[1,*], **Raushan Kumar**[1], **Prabhash Kumar Pandey**[1], **Abhishek Kumar Singh**[2] and **Nidhi Gupta**[3,4]

[1] *Department of Biochemistry, University of Allahabad, Allahabad-211002, Uttar Pradesh, India*

[2] *Amity Institute of Neuropsychology and Neurosciences, Amity University, Noida-201313, Uttar Pradesh, India*

[3] *Department of Psychology, VBM College (J.P. University, Chapra), Siwan-841226, Bihar, India*

[4] *Department of Psychology, D.D.U. Gorakhpur University, Gorakhpur-273001, Uttar Pradesh, India*

Abstract: Neurodegenerative disorders (NDs) are one of the leading serious problems worldwide, not only for developed countries but also for developing countries. NDs can be described as a progressive loss of neurons of the central nervous system that leads to cognitive impairment in individuals. The generation of excess reactive oxygen species is one of the reasons for the pathogenesis of NDs. From the various study, it has been established that the use of antioxidants may reduce the onset of NDs. The treatment of these diseases is very costly; for example, the cost of AD worldwide is estimated to be~ $800 billion in 2015. Moreover, in 2017 the cost of PD is reported to have been greater than ~$14 billion in the United States. Now, the researchers have focused on the screening of phytochemicals that have a huge antioxidant effect and neuroprotective ability. Phytochemicals are plant-derived biochemical, and they are described to have a protective effect on oxidative stress (OS), inflammation and provide better mental health. In this chapter, we have incorporated some important phytochemicals that have a great capacity to protect our brain cells and slow down or inhibit NDs pathogenesis.

Keywords: Antioxidant, Neurodegenerative disorders, Neuroinflammation, Oxidative stress, Phytochemicals.

INTRODUCTION

Neurodegenerative disorders (NDs) are a vital problem in both developed and developing countries of the world. Neurodegeneration can be characterized by chronic progressive loss of neuronal cells of the central nervous system (CNS)

[*] **Corresponding author Shambhoo Sharan Tripathi:** Department of Biochemistry, University of Allahabad, Allahabad-211002, India; Tel: +91 8887899227; E-mail: shambhudna@gmail.com

Sachchida Nand Rai (Ed.)

that culminated in functional and mental impairments [1]. Neurodegeneration is a consequence of elevated reactive oxygen/nitrogen species (RO/NS) formation, protein misfolding or aggregation, failure of mitochondrial function, synaptic loss, and apoptosis in neuronal cells [2]. An elevated augmentation of protein aggregation influences the signaling in neuronal cells and is an essential reason for cell death [3]. Some biological agents, like viruses, are also able for neuronal loss and lead to neurodegeneration [4]. Similarly, in multiple sclerosis (MS), the pathological features involve the permeability of the blood-brain barrier (BBB), the destruction of the myelin sheath, damage of the axon, the formation of the glial scar, and the presence of inflammatory cells, mostly lymphocytes infiltrated into the CNS [5, 6].

Aging is also one of the vital causes of neurodegeneration [7]. Most of the aging-associated NDs are distinguished by the diseases-specific misfolded proteins in nerve cells [8, 9]. For example, Alzheimer disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) are characterized by the aggregation of beta-amyloid and tau/phosphorylated tau, α-synuclein, superoxide dismutase, and mutant huntingtin (Htt) proteins respectively [10].

According to an epidemiologically study, AD constitutes worldwide 60%-80% of all dementia and significant form of memory loss-related disorders, hitting an expected 24 million people globally [11, 12]. PD is on rank second in neurodegenerative disorder, and the prevalence of PD is considered to be 0.3% in the global population, ~1% in aged persons (>60 years), and ~3% in more than 80 years of peoples [13, 14]. The frequency of HD was found to be 4–8 in 100000 people in Europe [15]; there is little information regarding the epidemiology of ALS and MS in the world. There is a higher incidence in men compared to women (1.5:1), with an average age of onset between 58 and 60 years and mean survival of 3 to 4 years after diagnosis [16].

Based on the pathogenesis of NDs, there is a requirement for therapeutic interventions that can protect from the most common hallmark of NDs. Phytochemicals are naturally occurring chemicals that can be the most suitable therapeutic intervention for it. In this book chapter, we tried to cover most of the therapeutic role of phytochemicals in NDs.

PATHOGENESIS OF NEURODEGENERATION

In the pathogenesis of NDs like AD [17], PD [18], HD [19], ALS [20], *etc.*, the involvement of mitochondria is very obvious. The role of mitochondrial dysfunction is consists of respiratory chain malfunction and production of OS reduction in ATP generation, calcium signaling dysregulation, the opening of

mitochondrial membrane transition pore, a perturbation in dynamics of mitochondrial, and deregulated mitophagy [21, 22]. Most of the mitochondria's functions are interdependent and can be present together in a different mode in the various disorders [23]. OS is one of the primary causes for NDs and is a state in which the equilibrium between the ROS production and the antioxidant level is significantly disrupted, and as a consequence, cells undergo apoptosis [24, 25]. Excessive ROS production makes several changes in biomolecules function and contributes to the pathogenesis of NDs. ROS alters the biomolecules, *i.e*., protein, lipid, DNA, and RNA of the cells [26]. These changes are very useful biomarkers for the detection of NDs. The polyunsaturated fatty acids (*e.g.*, arachidonic acids and docosahexaenoic acids) are present in a sufficient amount in the brain, and due to ROS attack, they change into oxidized form (malondialdehyde and 4-hydroxynonenal). ROS converts protein through oxidizing both the backbone and the side chain into carbonyl form. Uncontrolled oxidation of lipid in the presence of excess OS promotes protein aggregation in the pathogenesis of NDs [27, 28]. During the pathogenesis of NDs, changes in protein due to OS are protein carbonylation, nitration, and chlorination that leads to change in protein structure and functions [29]. ROS also engages in the conversion of nucleic acids in several ways, causing DNA-protein crosslinks, breaks in the strand, and modifies purine and pyridine bases resulting in DNA mutations [30, 31].

AD is the most prevalent neurodegenerative disease, distinguished by gradual neuronal degeneration linked with the aggregation of extracellular amyloid (Aβ) protein, and intracellular tau tangles. AD brains are associated with ROS mediated-damage; there is an increase in levels of lipid peroxidation in the brain and cerebrospinal fluid of AD patients compared to healthy controls [32]. Moreover, the concentration of protein carbonyl is increased in the AD brain [29, 33]. There is also an increment in ROS-induced hydroxylated guanine in AD samples compared to controls [34].

After AD, PD is the second most prevalent neurodegenerative disease. It is characterized by a gradual decline of dopaminergic neurons in the substantia nigra (SN) and aggregation of the protein α-synuclein. In the PD brain, the concentration of the markers of lipid peroxidation increases significantly in the SN region of the brain [35, 36]. The presence of excessive protein carbonyl in the PD brain also signifies the ROS-induced injury [29, 37, 38], and there is some proof to recommend a function for nitration and nitrosylation of specific proteins due to RNS in the PD brain [39, 40].

CHAPTER 4

Therapeutic Potential of Vitamins in Parkinson's Disease

Prabhash Kumar Pandey[1,2,*], Shambhoo Sharan Tripathi[1], Jayant Dewangan[2], Ranjan Singh[3], Farrukh Jamal[4] and **Srikanta Kumar Rath[2]**

[1] Department of Biochemistry, Faculty of Science, University of Allahabad, Prayagraj, Uttar Pradesh, India

[2] Genotoxicity lab, Division of Toxicology and Experimental Medicine, CSIR-Central Drug Research Institute, Lucknow, India

[3] Department of Biotechnology, Choithram College of Professional Studies, Indore, Madhya Pradesh, India

[4] Department of Biochemistry, Dr.Rammanohar Lohia Avadh University, Faizabad, Uttar Pradesh, India

Abstract: Vitamins are naturally present in vegetables, spices, food supplements, and fruits. Vitamins can mitigate or prevent the pathophysiological phenomena involved in the progression of Parkinson's disease (PD). PD is a progressive and disabling syndrome that affects the person's quality of life by causing motor and non-motor disturbances and imposing an enormous burden on the caregivers. Oxidative stress (OS), neuroinflammation, mitochondrial dysfunction, and formation of free radicals are behind the PD. Various clinical scientific shreds of evidence explain the role of vitamins in the treatment of PD. Several cellular and animal-based experiments point out that proper intake of vitamins is helpful in PD treatment. The time, exact doses, and safety of regular consumption of these supplements still need to be explored more by the scientific community. A balanced diet with vitamins as supplements can boost up the current therapies used against the PD. Vitamins have the crucial antioxidant property that acts against the OS, thus helps in PD treatment. Through different molecular mechanisms, these vitamins protect dopaminergic neurons. There is a need for a cure against the PD. A promising approach to cure this disease by natural means, such as vitamins, has been focused throughout this chapter. In this book chapter, the authors collected the scientific evidence available throughout the various experimental platforms and literature related to the functional role of vitamins in the improvement of the clinical framework of PD patients.

Keywords: Antioxidant, Lewy bodies, Neuroprotection, Neurotoxicity, Oxidative stress, Parkinson's disease, Substantia nigra, Vitamins.

[*] **Corresponding author Prabhash Kumar Pandey:** Department of Biochemistry, Faculty of Science, University of Allahabad, Prayagraj, Uttar Pradesh, India; Tel: +91 6394252573; E-mail: prabhashpandey@allduniv.ac.in

Sachchida Nand Rai (Ed.)

INTRODUCTION

Among neurodegenerative diseases, Parkinson's disease (PD) in aged people is widespread. Both the environmental and genetic factors are involved in the onset and progression of PD [1]. Among these factors, improper function of mitochondria and oxidative stress (OS) are the main factors that trigger the PD [1, 2]. PD affects 1-2% of the population older than the age of sixty, along with Alzheimer's [3]. Retrogression of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the locus coeruleus mainly trigger PD [4]. Locus coeruleus causes psychological effects, and the SNpc controls motor activity. The presence of Lewy neuritis and Lewy bodies (LB) in the brain represents the progression of PD [5]. Protein agglomerations such as parkin, alpha-synuclein, and some other proteins form the LB. In the different parts of the brain, these LB are present in the cytoplasm of the dead neurons [6]. Agglomerations of proteins form the large insoluble fibrils, which play a significant role in PD [7].

Different molecular mechanisms are involved in PD's pathophysiology, and they are all linked to each other [6]. In PD patients, many non-motor symptoms like olfactory dysfunction, sleep disorders, cognitive decline, constipation, and autonomic symptoms appear before the motor symptoms [8, 9]. OS is the leading cause behind PD's pathophysiology; therefore, those strategies regulating redox balance must come into practice for the treatment of PD [5].

Neuronal mitochondrial dysfunction is behind the pathophysiology of PD. Abnormal production of α-synuclein can cause mitochondrial dysfunction, leading to OS and neuronal degeneration in PD patients [10, 11].

To hold back the motor disorders, restoration of the dopamine level in the striatum is the turning point in PD treatment [12]. Treatment with the levodopa helps in peripheral dopamine metabolism. Levodopa smoothens the bioavailability of dopamine, thus lowering the motor complications [13, 14].

Vitamins have beneficial anti-oxidative as well as gene expression regulating tributes [15]. These marvelous properties of vitamins show their usefulness against the PD. Vitamins counteract or mitigate PD's pathophysiological phenomena, thus improving PD patients' cognitive functions and learning process [16]. Several clinical studies suggest that vitamins slow down PD progression in human beings; therefore, these nutrients can pretend as an adjuvant in the treatment of PD [17]. PD treatment is a challenging task, and current strategies to treat the PD can only relax the clinical symptoms, and they are not capable of

stopping the PD progression. In this book chapter, the biological interconnections between PD and vitamins and their therapeutic role in PD treatment have been discussed in detail.

ROLE OF OXIDATIVE STRESS IN THE PATHOGENESIS OF PD

Production of reactive oxygen and nitrogen like oxidative entities damage the imbalance between the antioxidant and oxidative systems, and as a result, OS happens [18]. OS actively participates in many physiological events of the organism. OS facilitates both the process of xenobiotic metabolism and the production of biologically active substances. It also kills the pathogenic microorganisms *via* phagocytosis [15]. OS can modulate the nucleic acid, takes part in the protein denaturation, damages the cellular membrane, *etc* [15]. Various studies suggest that reactive oxygen species (ROS) generated by the OS causes the death of neurons, and it is the main culprit behind PD's onset and progression [19, 20]. The respiratory chain of mitochondria is the leading site of ROS [21]. A clinical study by Schapira *et al.* [14, 22] shows that in the substantia nigra of PD patients, mitochondrial dysfunction happens. Accumulation of iron in substantia nigra of PD patients can trigger molecular oxygen and hydrogen peroxide production through the Haber-Weiss reaction [23]. Hydrogen peroxide produces hydroxyl radical, which is highly toxic. Severe oxidative damages occur due to this radical in cellular components [23]. Oxidation of dopamine and its metabolites reduces the activity of mitochondrial complex I [24]. Reduced glutathione boosts the generation of ROS [25]. Dopaminergic neurons become more susceptible after the production of their metabolites.

Accumulation of proteins, nonproper functioning of mitochondria, and DNA damage are severe intracellular events. OS initiates these processes, which lead to neuronal loss and PD [15]. Targeting these events can be beneficial in the treatment of PD. Vitamins could be a better way to treat the PD because these vitamins are the key to several biochemical pathways. In almost all tissues, vitamins act as enzyme cofactors [26]. These vitamins improve the nervous and immune system, regulate metabolism, and control cell growth and cell division events [26].

THEATRICAL ROLE OF NEUROINFLAMMATION IN THE PATHOGENESIS OF PD

In the pathogenesis of PD along with the OS, neuroinflammation also participates. It enhances the microglial activity and increases the production of pro-inflammatory and toxic mediators [27]. Insoluble fibrils trigger the activation of

CHAPTER 5

Potential of Gut Microbiome in the Diagnosis and Treatment of Alzheimer's and Parkinson's Disease

Nilofar Khan[1] and **Ravishankar Patil**[1,*]

Amity Institute of Biotechnology, Amity University, Maharashtra 410206, India.

Abstract: Neurodegenerative diseases (NDD) are a heterogeneous group of disorders characterized by a progressive, selective loss of physiologically related neuronal systems. Some prominent diseases include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Multiple Sclerosis (MS), and Huntington's disease (HD). It is believed that oxidative stress-induced cellular degeneration, inflammation, mitochondrial involvement, and dysfunction are important aspects in the pathogenesis of NDDs. Despite many decades of research and intensive studies, it has been an unending struggle to discover the root cause and a cure for these life-threatening ailments. However, the emerging domains of research provide evidence that probiotics and human gut microflora have a peculiar relationship with health and the pathogenesis of several diseases, including NDDs.

Microbiome and nutrients have a profound impact on the brain by influencing their development and function in health and diseases. The gut ecosystem and any modulation thereof exhibit a significant impact on the physiological and psychological health of an individual. The present chapter discusses the effect of the beneficial gut microbial community *versus* pathogens on the overall human health and its role in the development, diagnosis, and management of NDDs, especially Alzheimer's disease (AD) and Parkinson's disease (PD). Furthermore, the potency of probiotics and prebiotics as a gut-friendly therapeutic agent to treat these disorders is highlighted.

Keywords: Alzheimer's disease, Antioxidant, Gut microbiome, Gut-brain axis, Neurodegenerative diseases, Parkinson's disease, Prebiotics, Probiotics.

INTRODUCTION

Neurodegenerative diseases are ailments associated with the central nervous system (CNS), identified as chronic and progressive, and are indicated by the loss of neurons from specific areas of the brain [1]. The most communal NDDs are Alzheimer's disease (AD) and Parkinson's disease (PD). The progressive loss of neuronal cells and synapses, resulting in memory loss, poor learning, and

* **Corresponding author Ravishankar Patil:** Amity Institute of Biotechnology, Amity University, Maharashtra, 410206, India; Tel: +91 8999754168; E-mail: ravishankarpatil1@gmail.com

Sachchida Nand Rai (Ed.)

cognition, are the major characteristics of AD [2]. The depletion of acetylcholine level is the main molecular symptom of AD. Two critical hypotheses of AD pathogenesis is amyloid-beta (Aβ) [3] and tau [4]. Moreover, lifestyle factors such as being sedentary, stress, poor diets, and tobacco and alcohol consumption are also contributing factors in AD development [2, 5]. PD is considered the second most common NDD after AD. The confirmatory sign of PD is the depletion of dopaminergic neurons present in the substantia nigra region of the brain. The primary symptoms of PD are related to movement and balance (motor symptoms); however, secondary symptoms are also found, such as depression, dementia, hyposmia, chronic fatigue, constipation, loss of smell sense, and sleep disturbance [6].

Though numbers of drugs are in practice for the management of either AD or PD, no single one has proved to be effective for their complete cure. Hence there is a necessity for novel potent, and safer therapies that could offer symptomatic relief along with prevention of disease pathogenesis and progression. Recent research suggests that different disorders of the central nervous system (CNS) have a strong connection with gut microbiota *via* the enteric nervous system (ENS). Scientific literature proved that, in the diseased subject, there is a tremendous change in gut microbiota, which might be accountable for the increasing severity of illness. A decrease in gut-friendly microbes (For example, *Lactobacilli, Bacteroides, Prevotella, Bifidobacterium, etc.*) and an increase in pathogenic microbial population (For example, *Enterobacteria, Streptococci, Staphylococci, Shigella, H. pylori, etc.*) in case of AD and PD have been studied in detailed [7 - 13]. Gut microbiota affects brain functioning through the Gut-Brain Axis (GBA) in normal as well as diseased conditions. The microbial dysbiosis alters gut permeability, increases chronic inflammation, and triggers AD development [14 - 16]. A number of deadly pathogens, including *Staphylococcus aureus,* and *Mycobacterium tuberculosis,* synthesize amyloid protein, a protein having a key role in plaque formation in AD [17, 18]. In PD, gut microbes affect dopamine synthesis, α-synuclein deposition, increases oxidative stress, local inflammation, intestinal permeability, and causes constipation [19]. Current research suggests that dysfunction of gut microbiota can be explored for the early diagnosis of PD [19], and precise modulation of gut microflora in the diseased condition could help for effective management of disease pathogenesis as well as progression.

The present chapter discusses pathogenesis, prevalence, symptoms, and current therapies of AD and PD (in brief). More efforts have been taken to review the literature on the interaction of gut microbiota with CNS and its further involvement in the pathological process of AD and PD. Also, the potential of probiotics and prebiotics as therapeutic agents is discussed in deriving possible

treatment strategies to combat these NDDs by balancing the gut microbiome ecosystem.

ALZHEIMER'S DISEASE: PATHOMECHANISM, PREVALENCE, SYMPTOMS, AND TREATMENT

Alzheimer's disease (AD) is an NDD, causing a chronic and exponential loss of function and neuronal degeneration along with psychological distress [20]. It is associated with tau and amyloid peptide deposition in parts of the brain, which causes neurons to lose their function, mostly affecting neocortical structures [21]. The hallmark of AD is neuritic plaques and neurofibrillary tangles pertaining to amyloid-beta peptides (Aβ) accumulation in tissues of the brain and cytoskeleton changes caused by the hyperphosphorylation of tau protein present in the neurons [22]. The cognitive symptoms of AD are short-term memory, praxis, and executive and visuospatial dysfunction [23]. There are various beta-amyloid isoforms that vary depending on the amino acids present on the C-terminal. However, Aβ1−42 peptides play a vital role in AD pathogenesis [24]. The age, genetic constructs, and environmental factors impart a shift in metabolism that catalyzes the progression of amyloidogenesis of APP (Amyloid precursor protein) in deteriorating the physiological pathways, thereby promoting the APP cleavage using BACE-1 (beta-secretase enzyme) [25]. This particular reaction is the prime backbone of Aβ production [25]. The neurotoxic potential exuded by the Aβ peptides aid their aggregation into oligomers (insoluble) and protofibrils. Additionally, depleting Aβ from the brain causes their accumulation outside neurons, thereby triggering cascades leading to cytoskeletal modification, neural dysfunction, and finally, apoptosis [26].

Recent studies propose that AD may be categorized into three clinical stages:
(i) pre-clinical symptoms of AD, last for many decades until Aβ accumulation and their excessive production; (ii) early-stage pathology is the pre-dementia phase; (iii) Aggregation of neuritic plaques along with neurofibrillary tangles in certain areas of the brain, clinically defined stage of AD is assumed [27].

Prevalence of AD

Millions of people are affecting by AD, and notably, it is the most dominant cause of dementia (around 60-80%). However, delaying the onset of symptoms by a year significantly reduces the AD prevalence by more than 9 million cases over the next 4 decades [28]. Autopsies suggested that the neuropathological changes observed in patients with AD in developed countries are similar to the qualitative changes observed in developed countries [29].

CHAPTER 6

Therapeutic Efficacy of Mushroom in Neurodegenerative Diseases

Ankita Kushwaha[1,*], Vivek K. Chaturvedi[2], Sachchida Nand Rai[2], Sanjay C. Masih[3] and **M. P. Singh[2]**

[1] *Centre of Biophysics, Ewing Christian College, Prayagraj-211003, India*

[2] *Centre of Biotechnology, University of Allahabad, Prayagraj-211002, India*

[3] *Department of Zoology, Ewing Christian College, Prayagraj-211003, India*

Abstract: Mushrooms are used not only for culinary purposes, but also for the treatment of various chronic diseases. It shows vital therapeutic activity in several neurodegenerative disorders such as, Alzheimer's and Parkinson's diseases. These diseases are non-communicable as well as age-related. Currently, no drug therapy is available to treat such neurodegenerative disorders; instead, it is best to delay progression of these diseases. Accumulated evidence has suggested that culinary or medicinal mushrooms may play a significant role in the prevention of these disorders, as mentioned earlier, and dementia. Therefore, daily consumption of mushrooms in the diet may improve memory and cognitive functions, including mushrooms such as, *Hericium Erinaceus, Ganoderma lucidium, Pleurotus giganteus, Dictyophora indusiata, Sarcodon scabrosus, Antrodia camphorata Termitomyces albuminosus, Paxillus panuoides, Mycoleptodonoides aitchisonii, Lignosus rhinocerotis,* and numerous other species. These mushrooms show potent antioxidative, anti-inflammatory, and memory-enhancing activities. This chapter deals with the therapeutic activity of mushrooms and their bioactive components for different neurodegenerative diseases. Thus, mushrooms can be considered supportive and promising candidates for treating or preventing neurodegenerative diseases.

Keywords: Anti-inflammatory, Antioxidant, Culinary mushroom, Neurodegeneration, Neuritogenic, Neuroprotection, Neurotrophic.

INTRODUCTION

Neurodegenerative diseases (NDs) are predominantly increasing, attributable, in part, to extensions of a lifetime, which in turn, poses a significant danger to human health. Unfortunately, many of these diseases will increase as the world population ages and is expected to double by 2050 [1]. There is no treatment for

[*] **Corresponding author Ankita Kushwaha:** Centre of Biophysics, Ewing Christian College, Prayagraj-211003, India; Tel: +91 8299620239; E-mail:eshacompact15@gmail.com

Sachchida Nand Rai (Ed.)

NDs that prevent progressive degeneration of the nerve cells [2]. Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia, and spinocerebellar ataxias are examples of neurodegenerative diseases affecting millions of people all around the world. Such conditions are different in terms of their pathophysiology, such as loss of memory, cognitive (called dementia), and other abilities that affect the daily activity of an individual (called ataxias) [3, 4]. Currently, therapeutic neuroprotective approaches are explored to target molecular mechanisms that give rise to neurodegenerative diseases. Oxidative stress and mitochondrial dysfunction are the two factors that play a crucial role in the development of neurodegenerative diseases. The generation of toxic reactive oxygen species (ROS) interrupts the normal cellular metabolism, which causes extensive damage to the cells and tissues, and also causes neuronal cell death, which ultimately leads to oxidative stress [5]. Disruption in the mitochondrial functions induces glutamate-induced neuronal neurotoxicity, as mitochondria help to regulate the cell-death process. Therefore, oxidative stress and a mutation in the mitochondrial DNA cause neurodegenerative disease [6]. This chapter focuses on alternative drug therapy by daily intake of various culinary and medicinal mushrooms in the diet, leading to a delay in the development of neurodegenerative diseases. Mushrooms are macrofungi placed in the subkingdom of Dikarya, phyla Basidiomycota, and Ascomycota, whereas in class of Agaricomycetes and Pezizomycetes, respectively, they are also ubiquitous. Mushrooms are widely known not only for their nutritional properties, but also for their medicinal properties worldwide [7]. Mushrooms have a lot of beneficial compounds, such as, free radical scavengers, anti-apoptotic factors, and stimulators of nerve growth factors (NGF). These compounds directly exert positive effects on the brain. Thus, they serve as a “neuro-nutraceuticals” that protect the neuronal cell both *in vivo* and *in vitro.*

NEUROPROTECTIVE EFFECTS OF MUSHROOMS AGAINST NEURODEGENERATIVE DISEASE

Currently, the number of mushrooms estimated on the earth's surface are 150,000–160,000, although only 10% of the species are known [8]. They are known for their medicinal properties, excessive vitamins, free radical scavenger's antioxidant food supplements, and nitrosative stress to degenerate the metabolic processes [9]. The present section deals with the neuroprotective effects of mushrooms and their molecular mechanism against neurodegenerative disease. *Hericium Erinaceus is* also known as Lion's mushroom or Pom Pom mushroom, and it has been eaten for several years in Asian countries. Hericenones, a benzyl alcohol derivative (A-H), and Erinacines (A-K and P-Q) are two bioactive 2º

metabolites from fruiting bodies(basidiocarps) and mycelium, respectively [10] (Table **1**). Hericenones A and B were reported earlier, in the 1990s, but no neurite outgrowth NGF activity was reported. Moreover, in Hericenones C-H, *in vitro,* the biosynthesis of NGF was documented [11], whereas, Hericenones I and J and 3-hyrdoxyhericenone F, were reported in 2008. However, only 3-hydroxyhericenone showed a protective function against the ER stress-dependent neuro2a cell death. Erinacines A-C was an intense stimulation of the NGF activity [12]. The bioactive compound Dilinoleoyl Phoshatidylethanolamine (DLPE) from basidiocarps of *H. erinaceum* reduced the ER stress-dependent neuro2a cell death. Nagai *et al.* [13], also reported that 100 ng/ml DLPE from *H.erinaceum* significantly reduced the cell viability of Neuro2a cells, when treated with tunicamycin; thus, cell death occurred *via* the protein kinase C pathway (PKC). When the oral administration of *H. erinaceum* in the rat's brain was studied, significantly increased lipoxin A4 (LXA4) protein (anti-inflammatory properties) was found in the cortex and hippocampus region of the brain. Moreover, LXA4 upregulation was associated with the increased expression of cytoprotective proteins such as heat shock protein 70 (Hsp70), hemeoxygenase-11(HO-1), and thioredoxin (TRX), as investigated by Salinaro *et al.* [14]. *T. albuminous* is known as Termite Mushroom or “Ji Zong” mushroom in Chinese and consumed in countries such as China, Japan, and Chile. Cerebrosides and termitomycesphins (A-H) were bioactive compounds, extracted from the dried basidiocarps of *T.albuminosus*. When 10 µg/ml of termitomycesphins (A-D) was treated for six days, it induced neurite outgrowth of PC12 cell by 20% and 25%, whereas, 1 µM termitomycesphins G and H did the same in only for 48 hours [15, 16]. Choi *et al.* also investigated termitomycamide (A-E), which was a fatty acid amide. When 0.1 µg/ml of termitomycamide B and E was treated, it significantly reduced ER stress-dependent Neuro2a cell death by 20%. *M. aitchisonii,* also known as “Bunaharitake” mushroom in Japan, is cultivated on dead broadleaf trees in Asia and is well known for its beneficial effects of treating persistent diseases. There was *in-vitro* investigation of 0.6 µM of 5-hydroxy-4-(1-hydroxyeth-l)-3-methylfuran-2(5H)-one and 5-phenylpentane-1,3,4-triol; they were treated for 24 hours. It was observed that the two above-mentioned bioactive compounds protected against Endoplasmic Reticulum (ER) stress-dependent Neuro2a cell death [17]. However, when 0.1 µg/ml of other bioactive compounds such as 3-(hydroxymethyl)-4-methylfuran-2(5H)-one and (3R,4S, 1'R)-3-(1’-hydr-xy-ethyl)-4-methyldihydrofuran-2(3H)-one were treated for 24 hours, they showed significantly reduced tunicamycin-induced neuronal cell death, which signified their protective effects against ER stress-dependent Neuro2a cell death [18].

CHAPTER 7

Advances in Experimental Animal Models Provide Insights into Different Etiology and Mechanism of Multiple Sclerosis to Design Therapeutics

Sourodip Sengupta and **Jayasri Das Sarma***

Department of Biological Sciences, Indian Institute of Science Education and Research Kolkata (IISER-K), Mohanpur, Nadia, West Bengal-741246, India

Abstract: Myelin covering of axons in the central and peripheral nervous system helps in faster propagation of neuronal action potentials. Demyelination is a neurodegenerative process in which the axons lose their myelin coverings, exposing the axons to surroundings and leading to a reduction in neuron-to-neuron communication. Several demyelinating diseases exist in humans, and one of the most frequently occurring demyelinating disease of the CNS is multiple sclerosis (MS). Although more than 2.3 million people suffer from MS globally, the disease etiology is still unknown, impeding the development of effective therapeutics. The available treatments are based on disease-modifying therapy to reduce or moderate the symptoms and slow the disease progression; however, none can cure the disease. One key to better design therapeutics is to understand the cellular and molecular mechanisms of MS by developing reliable model systems. Human studies have their own limitations, such as limited access to patient tissues. Moreover, genetic variability makes it difficult to identify the triggers of MS. This calls for the development of reliable experimental animal models to understand MS pathogenesis better. There is no exclusive experimental model that covers the entire gamut of the disease. In this chapter, we will discuss experiment autoimmune encephalomyelitis (EAE), Theiler's murine encephalomyelitis virus (TMEV), and mouse hepatitis virus (MHV)-induced models of demyelination that mimic specific histopathological and neurobiological aspects of multiple sclerosis. The present understanding of MS as an autoimmune disease mediated by self-reactive T-cells comes mainly from studies on the EAE model. Further, viral-induced demyelination models have provided valuable insights into a better understanding of MS. Studies in the TMEV model have demonstrated molecular mimicry and epitope spreading as major mechanisms of virus-induced neuroinflammation. Our knowledge of immune-mediated CNS damage has been further enhanced by studies on MHV-induced neuroinflammatory demyelination, suggesting macrophage-mediated myelin stripping in neurodegeneration. While the limitations of these models of MS are obvious, appropriate use of this model has led to the development of clinically useful drugs for the treatment of this devastating disease.

* **Corresponding author Jayasri Das Sarma:** Indian Institute of Science Education and Research Kolkata IISER-K), Department of Biological Sciences, Mohanpur, Nadia, West Bengal-741246, India; Tel: +91 7003514069; E-mail: dassarmaj@iiserkol.ac.in

Sachchida Nand Rai (Ed.)

Keywords: Demyelination, EAE, MHV, Multiple sclerosis, Neurodegeneration, Neuroinflammation, TMEV.

INTRODUCTION

The brain, which forms part of the Central nervous system (CNS), is an important organ that controls other organs through nerve connectivity and conduction of nerve impulses [1].

Myelin covering of axons in the central and peripheral nervous system (PNS) helps in faster propagation of neuronal action potentials. Demyelination is a neurodegenerative process in which the axons lose their myelin coverings, exposing the axons to surroundings and leading to a reduction in neuron-t--neuron communication [2]. Several demyelinating diseases exist in humans, including:

- Optic neuritis, Neuromyelitis Optica (Devic's disease)—inflammation of the optic nerve.
- Transverse myelitis—inflammation of the spinal cord.
- Acute disseminated encephalomyelitis—inflammation of the brain and spinal cord.

One of the relatively common demyelinating diseases of the CNS is multiple sclerosis (MS). MS is a chronic demyelinating disease of the CNS where the myelin sheath gets damaged and forms scar tissue termed sclerosis. The resulting nerve damage disrupts the transmission of nerve impulses [3].

Earlier notions visualized the brain as an immunologically protected site with its immune surveillance system in the form of glial cells and restricted communications with the peripheral immune system(PIS). However, the previous notion has been proved wrong with the understanding that there exists a bi-directional communication between the PIS and the brain [1]. In general, inflammation in the CNS, commonly termed neuroinflammation, serves as a protective mechanism [1]. However, prolonged neuroinflammation is a responsible factor for the onset of neurodegeneration and neuronal losses associated with it. Neurodegeneration is a condition in which neurons suffer structural and functional alterations, resulting in reduced survival and increased neuronal death [1].

Recent findings showed the presence of inflammation in the brain regions of autopsy samples from MS patients, indicating a link between inflammation and

neurodegeneration [4]. Further studies revealed the presence of antibody deposits within MS lesions in the brain from the progressive disease phase [5]. These observations are indicative of a connection between neuroinflammation and neurodegeneration in MS. However, it is unclear whether the primary cause for neurodegeneration is neuroinflammation or it is only a secondary effect.

CLASSIFICATION OF MS

Globally, more than 2.3 million people suffer from MS. Most diagnosed patients fall within the age bracket of 20-50 years, and about two-thirds are women. Periods of active MS symptoms are called relapse or attacks, while the remission period follows no attack. In relapse-remitting MS (RR-MS), patients have attacks followed by partial or total remission that may extend between months to years. Most people are diagnosed at the relapse-remitting stage [3].

In primary progressive (PP-MS) disease conditions, patients miss the remission phase, and symptoms worsen steadily from the onset, which is usually observed in 10-15% of cases [3]. PP-MS is generally seen in older patients, suggesting that age could be a determining factor for disease progression [6]. In the majority of RR-MS patients, the disease may become progressive after an initial remission period, as seen in secondary progressive (SP) MS [2, 7].

ETIOLOGY OF MS

The exact cause of MS is not known yet, and a multitude of factors such as genetic, environmental, and autoimmunity can be responsible for the disease onset. The rate of MS incidence is relatively low in childhood. Chances of MS increases post 18 years of age, with maximum occurrence observed in people falling between 25-35 years of age (women are at a higher risk than men). The appearance of MS slowly declines with age, becoming rare at age 50 and older [8].

While MS is prevalent in the US, Canada, Europe, New Zealand, and parts of Australia, it is relatively scarce in Asia and is generally limited to the tropics and subtropics. In temperate regions, the incidence of MS increases with latitude [8]. Epidemiological studies suggest a correlation between disease prevalence and exposure to sunlight [9]. Sunlight exposure is a significant source of vitamin D for most people. As the amount of sunlight decreases at higher latitudes, a greater incidence of MS could be due to vitamin D deficiency. A fascinating observation is that the risk of MS declines among individuals migrating from high- to low-risk areas but does not necessarily increase with migration in the opposite direction

CHAPTER 8

Novel Therapeutic Targets in Amyotrophic Lateral Sclerosis

Priyanka Gautam, Mukesh Kumar Jogi and **Abhishek Pathak***

Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Abstract: Amyotrophic Lateral Sclerosis is an adult-onset, irremediable, and fatal neurodegenerative disease marked by the advancement in the loss of motor neurons in the spinal cord, brain stem, and motor cortex. Etiology is blurred, but it is thought to be multifactorial, which contributes to the heterogeneity and complexity of the disease. Core knowledge of primary etiology and pathological mechanisms can pave the way towards treatment. This chapter examines mechanisms that may contribute to motor neuron degeneration, among which oxidative stress, mitochondrial dysfunction, protein aggregation, axonal transport are potential novel therapeutic targets for ALS treatment.

Keywords: Amyotrophic lateral sclerosis, Motor neuron, Neurodegenerative disease.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS), sometimes referred to as "Lou Gehrig's disease," is characterized by progressive deterioration of the upper motor (UMN) and lower motor neurons (LMN), which regulate muscle weakness and eventually leading to paralysis [1]. The initial presentation of ALS may vary among patients; some are present with spinal-onset disease, but others can present with bulbar-onset disease, which are characterized by dysarthria and dysphagia. In most patients, the root of ALS is mysterious; however, some individuals have familial disease, which is associated with changes in genes that have a variety of functions, including roles in non-motor cells. In familial ALS, some of the implicated genes are not fully penetrant, and with rare exceptions, the genotype does not necessarily predict phenotype [2].

Respiratory failure occurs in most patients within 2-5 years after diagnosis due to respiratory muscle involvement. Some patients may have a cognitive impairment,

* **Corresponding author Abhishek Pathak:** Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India; Tel: +91 8840139503; E-mail: abhishekpathakaiims@gmail.com

Sachchida Nand Rai (Ed.)

further adding to the damage. Only10% of the patients survive with 10 years of lifespan [3]. There has been a gradual increase over the past few years in ALS, although no unified hypothesis has been revealed for its pathogenesis. Most cases of ALS are sporadic (SALS), although some are classified as 'familial ALS' (FALS) because few causal genes have been identified in the last three decades. The study of these gene variants has led to many new pathophysiological concepts and new therapeutic approaches [4].

HISTORY

American baseball player Lou Gehrig was diagnosed with ALS, after which ALS is also known as Lou Gehrig's disease. His disease was under investigation for his immediate loss of performance in baseball, and as a result, there was an early withdrawal, and two years later, he died at the age of 37. Another renowned personality who was a British physicist was Stephen Hawking, diagnosed with ALS at the age of 21, and he lived over 70 years under palliative care [5].

EPIDEMIOLOGY

ALS incidence is 4.1-8.4 per 100,000 people in recent population-based studies [6]. The universal incidence of ALS has increased over the years, especially in Western societies. ALS is an uncommon disease, and its incidence is estimated to be 2-3 per 100,000 in Europe and 0.7–0.8 per 100,000 individuals in Asia [1]. The prevalence of ALS is higher in people aged over 50 years and is 6 per 100,000 of the total population. Only 10% of cases are familial (inherited from parents), and the remaining 90% of cases are sporadic. According to the Foundation for Research on Rare Diseases and Disorders [fRRDD], the frequency of ALS cases in India is 5 per 100,000, and the male to female ratio is 2:1 [5].

SIGN AND SYMPTOMS

Muscle weakness, torsion, and numbness are common symptoms found in both types of ALS that can lead to muscle detriments [7, 8]. ALS patients develop symptoms of dyspnoea and dysphagia at their most advanced stage [9]. The preparative characteristics of ALS are often elusive despite the fatal nature of the disease [10]. Unidentified symptoms delay the diagnosis of ALS, sometimes lead to false diagnosis as well. Retrospective reviews have demonstrated a delay in symptom diagnosis, which has not changed for more than a decade and ranges from 8.0 to 15.6 months [11, 12]. Fig. (**1**) shows the ALS patient's UL atrophy.

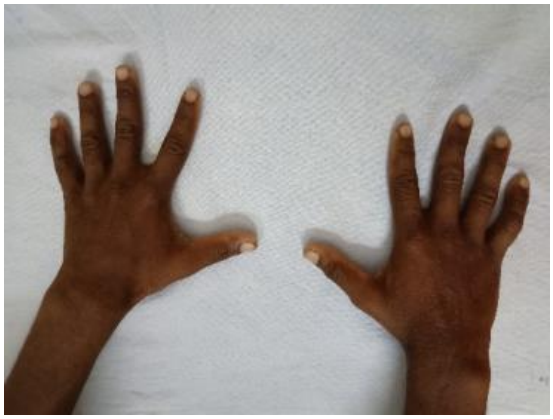


Fig. (1). ALS patients UL atrophy.

CLINICAL CHARACTERISTICS

The clinical diagnosis of classic ALS was found on the detection of progressive dysfunction of cortical UMNs and spinal LMNs in many body regions (mainly, limbs and bulb areas). Much of this presentation is redirected by the El Escorial criteria [13, 14]. In contrast, patients may present with less motor neuron symptoms, including fasciculation, numbness, and muscle wasting. Almost one-third of patients with ALS have bulbar-onset disease, which is characterized by progressive dysarthria following by dysphagia and is sometimes accompanied by emotional dysfunction. Limb-onset disease occurs in about 60% of cases, is usually asymmetrical in appearance, and first develops in the upper or lower limbs. About 5% of patients have respiratory problems, and these patients are often seen in cardiology and pulmonology clinics before being sent to neurology clinics [15]. Fasciculation is a symptom of ALS but are difficult to detect in some patients. Fasciculation arises in the axon of diseased motor neurons in ALS but not specific to the disorder; these include other chronic neurogenic disorders, endocrine/metabolic conditions in some normal people [16 - 18]. The emergence of multidisciplinary, exclusive ALS clinics has enhanced the quality of life and survival of ALS patients, with early non-invasive ventilation as one of the most vital determinants of survival; however, there is still no proper curable treatment for ALS patients [19]. Riluzole is the first FDA approved drug which is available for ALS patients and is believed to act by a variety of mechanisms by blocking the presynaptic release of glutamate, neutralizing voltage-dependent Na^+ channels, reducing hyperactivity, and inactivating K^+ channels, inhibiting kinase C and interfering with exciting transmitter-induced intracellular events; thus exhibiting a modest ability to slow down disease progression, especially when given early in the course of the disease [20].

CHAPTER 9

Impact of Nano-Formulations of Natural Compounds in the Management of Neuro degenerative Diseases

Hemraj Heer[1], Vishav Prabhjot Kaur[1], Tania Bajaj[1], Arti Singh[2], Priyanka Bajaj[3] and **Charan Singh[1,*]**

[1] *Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab-142001, India*

[2] *Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab-142001 Affiliated to IK Gujral Punjab Technical University, Jalandhar, Punjab-144603, India*

[3] *Instituite of Microbial Technology, Sector 39A, Chandigarh-160036, India*

Abstract: Neurodegenerative disorders (NDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), are caused by oxidative stress, inflammation, and proteinopathy. These are further characterized by loss of neurons and, consequently, impaired cognitive functions. However, the exact mechanisms of the pathogenesis of these diseases are still unknown. Nowadays, natural compounds like curcumin, quercetin, resveratrol, and piperine, among others, have been explored for the treatment and prevention of neurological disorders. There are various *in vivo* studies and clinical trials conducted for alleviating neurological disorders using natural compounds encapsulated in nanocarrier systems. Nanoparticles such as lipidic, polymeric, quantum dots help to enhance the bioavailability, specificity, and targeted delivery of these compounds in the brain. Various simple and reproducible methods are reported to synthesize the nanoparticles in the literature. In this chapter, we will explore the role of nanotechnology and natural compounds to treat and prevent neurodegenerative disorders.

Keywords: Nanotechnology, Nanoparticles, Natural compounds, Neurodegenerative disorders, Targeted delivery.

INTRODUCTION

Neurodegenerative disorders affect millions of people worldwide every year. The vitality and functionality of the nerve or central nervous system (CNS) are affected partially or completely due to Alzheimer's disease (AD), Parkinson's

* **Corresponding author Charan Singh:** Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab-142001, India; Tel: +91 9817067168; E-mail: c.singhniper09@gmail.com

Sachchida Nand Rai (Ed.)

disease (PD), Huntington's disease (HD), Multiple Sclerosis (MS), and Amyotrophic Lateral Sclerosis (ALS). At the same time, it offers a great challenge owing to poor prognosis *vis-a-vis* the rest of the body part [1]. The measure cause of neurodegeneration is the loss of myelin sheath, protein degradation, mitochondrial dysfunction, accumulation of mutated proteins, family background along with some environmental factors. Furthermore, aging is another important mechanism that is reported in various brain disorders [2]. AD is considered the most common form of dementia in which cognitive functions alter. As per Alzheimer's Disease (AD) Report 2019, around 6 million Americans are living with Alzheimer's dementia [3]. Extracellular accumulation of β-amyloid (Aβ) peptide and deposition of tau-protein cause neuroinflammation in the brain and, consequently, synaptic impairment and neuronal loss [4]. PD is considered the second most prominent ND. This occurs due to the development of bradykinesia and tremors of cardinal motor functions in the *substantia nigra* [5]. The major hallmark of PD is reducing uptake of dopamine by dopaminergic neurons due to the low level of dopamine transporters (DATs). Additionally, the deposition of α-synuclein in Lewy bodies is another cause of PD [6]; however, their actual mechanism to produce Parkinson's is not fully understood yet [7]. Huntington's disease (HD) is another autosomal ND that usually develops due to mutation in genes located on chromosome 4. This genetic disorder is characterized by repeated expression of CAG (cytosine, adenine, and guanine) tri-nucleotides. The HD progresses due to the accumulation of Huntington mutated protein as a result of the repeated unit of CAG [8]. Behavior abnormality and change gate are the common symptoms in this disease [9].

Some of the common factors involved in neurodegeneration are the level of glutamate, free radical generation, the concentration of reactive nitrogen species, proteinopathy, nuclear pore anomalies, and inflammation, and calcium ion [10]. Glutamate is an excitatory neurotransmitter in the brain, and its overexcitation activates N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-me-hyl-4-isoxazole propionic acid (AMPA), eventually leading to the apoptotic destruction of neurons. Additionally, proteinopathy is responsible for the accumulation of misfolded proteins such as α-synuclein and Aβ in PD and AD, respectively [11]. Elevated levels of these proteins are reported in the clinical conditions of neurodegeneration. Moreover, free radical and reactive oxygen species holds the lion's share. These are the radicals with lone pairs of electrons that can trigger free radical cascade and neuron damage by disturbing its biochemistry [12]. The influx and efflux of proteins like nucleoporins (Nups) and Ran GTPase-activating protein (RanGAP) across the nuclear barrier play a key role in the normal functioning of the neuron [13]. Hence, impairment of influx and efflux proteins causes damage to the nuclear physiology, which subsequently induces neurodegeneration. In recent times, neuroinflammation has been another

dimension in the aetiology of various NDs that has been under investigation. Scientists have found the significant role of inflammatory mediators and calcium in the progress of neuronal loss [14]. **C**alcium is an important mediator involved in neuronal physiology and integrity. Hence, abnormal calcium transport and barrier function can lead to neuroinflammation, apoptosis, and loss of neurons [15].

NEUROPROTECTIVE POTENTIAL OF NATURAL PRODUCTS

Tremendous efforts have been made to introduce new CNS drugs for effective treatment as available drugs are mainly used for symptomatic relief. However, designing permanent therapeutics or preventive medicines for curing and/or preventing neurodegeneration is still a great challenge. Various synthetic and semisynthetic therapeutic agents have remarkable therapeutic effects in disease management, but severe side effects limit their use [16]. Nowadays, natural products have gained attention as new promising therapeutic agents due to their neuroprotective, antioxidant, and anti-inflammatory activities [17]. Ample reports suggest the role of inflammatory markers and reactive species for neuronal pathology through biological pathways [13]. Therefore, inhibition of these pathways using natural compounds might play a key role in the management of NDs [18]. Of late, fighting NDs using herbal drugs has become a thrust area. After The 'Green' movement in Western society, the majority of health concerned people in these countries utilized phytomedicine for primary healthcare as various plants-based bioactives were used in traditional medicine to cure neurodegenerative diseases. The natural product contains diverse phytoconstituents in the form of fatty acids, sterols, alkaloids, flavonoids, glycosides, saponins, tannins, terpenes, *etc.* These possess strong therapeutic potential to treat different types of diseases [19]. There are more than 120 medicinal plants and their natural compounds that are used to cure neurodegenerative disease, and they show promising neuropharmacological activity [20]. A few of them are Curcumin, *Ginkgo biloba, Panax ginseng, Bacopa monniera*, Withania somnifera, Polyphenols (Epigallocatechin-3-galate (EGCG) Resveratrol), Flavonoids Quercetin Terpenoids, and Saponins [21 - 34].

APPROACHES FOR CNS TARGETED NATURAL COMPOUNDS DELIVERY

In this modern era, even though sufficient knowledge and new inventions in the field of medicine and drug delivery techniques are available, still the whole world is fighting with the most complex neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's disease, Multiple Sclerosis, and Amyotrophic Lateral Sclerosis, *etc.* The limited clinical interventions in

CHAPTER 10

Recent Advancement in the Nanoparticles Mediated Therapeutics of Parkinson's Disease

Vivek K. Chaturvedi[1], Payal Singh[2] and **M.P. Singh[1,*]**

[1] *Centre of Biotechnology, University of Allahabad, Prayagraj-221002, India*

[2] *Department of Zoology, MMV, Banaras Hindu University, Varanasi-221005, India*

Abstract: Nanoparticle plays a very effective role in the therapeutics of Parkinson's disease (PD). The blood-brain barrier (BBB) is the main barrier that prevents the efficiency of any therapeutic compound.Nanoparticles overcome this problem by crossing the BBB. Recently many nanoparticles show promising responses in PD. Silver, gold, and many other nanoparticles effectively prevent progressive neurodegeneration in PD. In this book chapter, we have included some recent development in the nanoparticles mediated therapeutics for PD.

Keywords: Gold Nanoparticle, Growth Factor, Nanoparticles, Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease of the aging population after Alzheimer's disease, which is characterized by specific motor as well as some nonmotor symptoms [1, 2]. Resting tremors, bradykinesia, postural imbalance, *etc.*, are the most common motor symptoms, while constipation, sleeping abnormalities, fatigue, *etc.* considered the nonmotor ones [3, 4]. Till now, the complete cure for this progressive disease is not possible; levodopa (L-Dopa) dependent therapy is one of the best treatments available that only use to manage the symptomatic response that ultimately cause L-Dopa induced dyskinesia upon prolonged use [5, 6]. In the last few decades, researchers have tried several alternative ways to combat this disease effectively. Herbal mediated therapy is the best example of PD therapy having minimum side effects [7]. *Mucuna pruriens*, *Withania somnifera*, *Tinospora cordifolia, etc.* are some common examples of herbal plant that shows the promising response in

* **Corresponding author M.P. Singh:** Centre of Biotechnology, University of Allahabad, Prayagraj-221002, India; Tel: +91 9415677998; E-mail: mpsingh.16@gmail.com

Sachchida Nand Rai (Ed.)

PD treatment with minimum side effect [8 - 12]. Some chemical compounds like Ursolic acid and Chlorogenic acid also exert significant neuroprotection for PD [13 - 15]. The blood-brain barrier (BBB) is the biggest culprit that minimizes the therapeutic response of the above-mentioned herbal plant and chemicals. Researchers have made an enormous attempt to resolve this barrier problem. Nanoparticles are the best way to overcome this problem because of the smallest size that easily penetrates the BBB and also causes minimal side effects with greater efficiency [16, 17]. Following this, we have discussed the nanoparticles-based therapy PD in the following paragraph.

NANOPARTICLES BASED THERAPY FOR PARKINSON'S DISEASE

Gold nanoclusters exhibited a strong therapeutic response in the Parkinsonian mouse model. In this study, the authors wanted to optimize the route for these gold nanoclusters (AuNCs) in the PD model. Different routes of administration, for example, intravenous, intraperitoneal, gavage, and intranasal injection, wereutilizedto find the efficacy of these nanoclusters. Different microscopies were usedto check the biodistribution of AuNCs in mice. Both *in vitro*(cells) and *in vivo* (mice) were used to assess the toxicity of AuNCs. In the mouse brain, intraperitoneal administration showed better bioavailability and half-life as compared to other routes. AuNCs easily crossed the BBB and were excreted by the kidney, and no toxicity was found in both cells and mice regarding these nanoclusters. Authors have concluded that the intraperitoneal route is the most effective one, which shows a better response in comparison with other routes of entry [18]. In the mouse model of PD, dextran-coated iron oxide nanoparticle improves the efficacy of human mesenchymal stem cells in the manifold. This stem cell can differentiate into dopaminergic neurons and also secrets various neurotrophic factors. Mesenchymal stem cells exhibit the ability to replace damaged neurons. Therefore, we can say that this dextran-coated iron oxide nanoparticle prevents the progressive degeneration of dopaminergic neurons indirectly by improving the function of mesenchymal stem cells [19]. Cerium oxide nanoparticles(CeO2NPs) showed the anti-PD potential in the 6-hydroxydopamine (6-OHDA) induced Parkinsonian rat model. Behavioral impairment was induced by this PD toxin OHDA which wassignificantly improved by these nanoparticles as demonstrated by an open field, rotarod, and stepping test. Also, CeO2NPs reversed the neurobiochemical abnormalities in the striatum. CeO2NPs decreased apoptosis and slightly ameliorated the dopamine level in the stratum. The authors have concluded the antiapoptotic and antioxidative activity in the 6-OHDA intoxicated model of PD [20]. Further study will be needed to confirm the same.

Growth factor (GF) based therapy shows a very promising response for the PD treatment [21]. Among different GF, glial cell-derived neurotrophic factor (GDNF) is the most studied one and also passed the double-blind clinical trial for PD [22]. GDNF's shorter half-life, rapid degradation rate, and limited capacity to cross the BBB reduces its success in clinical studies. One interesting study overcomes this BBB and other hurdles of GDNF. In this study, GDNF was encapsulated into chitosan (CS)-coated nanostructured lipid carriers, with the surface-modified with transactivator of transcription (TAT) peptide (CS-nanostructured lipid carrier (NLC)-TAT-GDNF) and administered *via* the intranasal route in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxicated mouse model of PD. This nanostructure improved the motor symptoms in the Parkinsonian model. In addition, the count of marker enzyme of PD pathogenesis, which is tyrosine hydroxylase (TH), also improved in striatum and substantia nigra by this GDNF coated nanostructure. This CS-NLC-T-T-GDNF can reverse the Parkinsonian symptoms and suggest an alternative and effective therapeutic option for PD [23].

Gold Nanoparticles (GNP) show a considerable amount of neuroprotective activity in the Parkinsonian model and *in vitro*. A study showed the potential of GNP on PC12 cells and in mice. GNP inhibited the process of apoptosis in PC12 cells and of dopaminergic neurons. A significant amount of GNP in the brain of the mouse showed that GNP effectively crosses the BBB. GNP showed potent neuroprotective activity in both model systems [24]. In 6-OHDA partially lesioned rats' model of PD, vascular endothelial growth factor (VEGF) and GDNF-loaded nanospheres show strong synergistic Anti-Parkinsonian activity. This synergistic combination might be used as an alternative option for PD therapy [25]. For the efficient intranasal delivery of rotigotine in the PD model, a study used biodegradable poly(ethylene glycol)–poly(lactic-co-glycolic acid) (PEG-PLGA) nanoparticles (NPs). These NPs effectively targeted the rotigotine into the brain, as suggested by the intranasal administration. This study explored the role of these NPs *in vitro* and *in vivo*. Both model studies show the beneficial response of NPs and warrant further study to confirm the same [26]. Metformin loaded polydopamine nano-formulation promoted the autophagic activity in the PD model by promoting enhancer of zeste homolog 2 mediated proteasomal degradation of phospho-α-Synuclein [26]. Intranasally administered selegiline nanoparticles (SNPs) showed its significant amount in the brain of the PD model. This SNPs intranasal delivery showed a very effective therapeutic response in PD compared to the oral route [27].

SUBJECT INDEX

I

K

L

M

N

O

P

Q

R

S

T

U

V

W

Y

Sachchida Nand Rai

Dr. Sachchida Nand Rai is a Postdoctoral Fellow at the center of Biotechnology, University of Allahabad, Prayagraj, India, since 2020.

Dr. Rai completed his graduate and postgraduate studies from V. B. S. Purvanchal University Jaunpur, India, and Ph. D. from Banaras Hindu University, Varanasi, India. His research interest includes herbal and chemical compounds mediated neuroprotection of Parkinson's and Alzheimer's disease.