INDOPATHY FOR NEUROPROTECTION: RECENT ADVANCES

Editors:
Surya Pratap Singh
Hagera Dilnashin
Hareram Birla
Chetan Keswani

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Edited by

Surya Pratap Singh
Department of Biochemistry
Institute of Science, Banaras Hindu University
Varanasi-221005, India

Hagera Dilnashin
Department of Biochemistry
Institute of Science, Banaras Hindu University
Varanasi-221005, India

Hareram Birla
Department of Biochemistry
Institute of Science, Banaras Hindu University
Varanasi-221005, India

&

Chetan Keswani
Department of Biochemistry
Institute of Science, Banaras Hindu University
Varanasi-221005, India

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Editors: Surya Pratap Singh, Hagera Dilnashin, Hareram Birla and Chetan Keswani

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FOREWORD

Exposure to plant-based phytochemicals can promote health and prevent chronic neurodegenerative diseases. Most traditional treatment prescriptions consist of a combination of several drugs. The combination of multiple drugs is thought to maximize therapeutic effectiveness by promoting synergies and improving or preventing potential side effects while targeting multiple goals.

Indopathy is a valuable source of information for discovering new remedies for a variety of human illnesses. The complex etiology of neurodegenerative diseases and the multifactorial effects of Indopathy and its active ingredients may give a broad perspective on traditional indian medicine in neuroprotection. Some indian medicinal plants and their active ingredients have shown promising results for oxidative stress, inflammation, apoptosis, and neurodegeneration in laboratory studies. Indopathy has excellent prospects for the treatment of neurodegenerative diseases and is considered to be effective in neuroprotection.

Combining modern molecular medicine principles with some ideas of traditional indian empirical medicine may be beneficial to translation medicine.

The proposed book focuses on indopathy for the treatment of neurodegenerative diseases. This book reviews a subset of traditional indian medicines and highlights their neuroprotective active ingredients for their antioxidant, anti-inflammatory, and cognitive-enhancing effects. This volume provides a comprehensive introduction to therapeutic options for some popular plant-derived neuroprotective agents. I congratulate the editor for synchronizing with global authorities on the subject to underline the upcoming challenges and present the most viable options for translating commercially viable ideas into easily affordable products and technologies.

I wish all the editors great success with the launch of this book and thank them for their dedication to plant-based neuroprotection around the world.

Dr. Amulya K. Panda
Former Director
National Institute of Immunology
New Delhi
India

PREFACE

With the rapid increase in life expectancy and the proportion of the elderly population, the global prevalence of various neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and Huntington's disease, is rising dramatically. The demographic trend of the aged population has attracted people's attention to the discovery and treatment of new drugs for age-related diseases. Currently, there are various drugs and treatments available for the treatment of neurodegenerative diseases, but side effects or insufficient drug efficacy have been reported. With a long history of herbs or natural compounds used in the treatment of age-related diseases, new evidence has been reported to support the pharmacological effects of Indopathy in ameliorating symptoms or interfering with the pathogenesis of neurodegenerative diseases.

Many indian medicinal plants have been used for thousands of years in indopathy. Amongst these are plants used for the management of neurodegenerative diseases, such as Parkinson's, Alzheimer's, loss of memory, degeneration of nerves, and other neuronal disorders by Ayurvedic practitioners. Though the etiology of neurodegenerative diseases remains enigmatic, there is evidence indicating that defective energy metabolism, excitotoxicity, and oxidative damage may be crucial factors.

This book summarizes the new therapeutic leads from herbal sources for various types of neurodegenerative diseases. Based on recent research, this book makes an effort to utilize existing knowledge of some popular medicinal plants, and their biologically active components have been discussed, especially those used in indopathy. Several promising plants such as *Withania somnifera, Bacopa monnieri, Centella asiatica*, and *Mucuna pruriens* are worth exploring for the development of neuroprotective drugs.

Surya Pratap Singh
Department of Biochemistry
Institute of Science, Banaras Hindu University
Varanasi-221005, India

Hagera Dilnashin
Department of Biochemistry
Institute of Science, Banaras Hindu University
Varanasi-221005
India
Hareram Birla
Department of Biochemistry
Institute of Science, Banaras Hindu University
Varanasi-221005
India
&

Chetan Keswani
Department of Biochemistry
Institute of Science, Banaras Hindu University
Varanasi-221005, India

ABBREVIATIONS

6-OHDA 6-Hydroxydopamine
ABC ATP-Binding-Cassette
AP-1 Activator Protein 1
ADP Adenosine Dinucleotide Phosphate
α-Syn Alpha-Synuclein
AD Alzheimer Disease
Aβ Amyloid-Beta
APP Amyloid-Beta Precursor Protein
ApoE Apolipoprotein E
ASC Apoptosis-associated Speck-like Protein comprising a Caspase Recruitment Domain
AIF Apoptosis-Inducing Factor
AI Artificial Intelligence
Bcl-2 B-Cell Lymphoma 2
Bax Bcl-2 Associated X
BACE1 Beta-Site Amyloid Precursor Protein Cleaving Enzyme 1
HEXA Beta Hexosaminidase A
HEXB Beta Hexosaminidase B
BBB Blood-Brain Barrier
BDNF Brain-derived Neurotrophic Factor
JNK c-Jun N-Terminal Kinase
CLR C-Type Lectin Receptor
Iba1 Calcium-Binding Adaptor Molecule 1
CAT Catalase
CNS Central Nervous System
CSF Cerebrospinal Fluid
CVD Cerebrovascular Disease
COPD Chronic Obstructive Pulmonary Disease
CELA3A Chymotrypsin-Like Elastase Family Member 3A
COX-2 Cyclooxygenase-2
CBG Cytosolic Beta Glucosidase
DAT DA Transporter
DAMP Damage-Associated Molecular Pattern

DMC Demethoxycurcumin
DA Dopamine
Daergic Dopaminergic
ERAD Endoplasmic Reticulum Associated Degradation
EDS Excessive Daytime Somnolence
EXOtic Exosomal Transfer into Cells
ERK Extracellular Signal-Regulated Kinases
FAD Familial AD
FDG-PET Fluorodeoxyglucose Positron Emission Tomography
fMRI Functional Magnetic Resonance Imaging
NG2 Glial Antigen-2
GDNF Glial-derived Neurotrophic Factor
GFAP Glial Fibrillary Acidic Protein
GBA Glucocerebrosidase
GSH Glutathione
HO1 Hemeoxygenase 1
HD Huntington's Disease
iPD Idiopathic PD
IGLV1-33 Immunoglobulin Lambda Variable 1-33
iNOS Induced Nitric Oxide Synthase
IRF3 Interferon Regulatory Factor 3
IL-1β Interleukin-1 Beta
IL-2 Interleukin2
KMO Kynurenine 3-Monooxygenase
LPH Lactase Phlorizin Hydrolase
LTF Lactoferrin
LRRK-2 Leucine Rich Repeat Kinase 2
LRR Leucin Rich Repeats
L-Dopa Levodopa
LBs Lewy Bodies
LRP-1 Low-Density Lipoprotein Receptor-Related Peptide 1
LSD Lysergic Acid Diethylamide
MRI Magnetic Resonance Imaging
mTOR Mammalian Target of Rapamycin
MPTP 1-Methyl-4-Phenyl-1, 2, 3, 6-Tetrahydroxypyridiine

MPP^+ 1-Methyl-4-phenylpyridinium
MCAO Middle Cerebral Artery Occlusion
MCI Mild Cognitive Impairment
MAPK Mitogen-Activated Protein Kinase
MAO-B Monoamine Oxidase B
MSA Multiple System Atrophy
NLR NOD-LRR-Containing Receptor
NEP Neprilysin Protease
NCAM Neural Cell Adhesion Molecule
NFTs Neurofibrillary Tangles
NADH Nicotinamide Adenine Dinucleotide
NO Nitric Oxide
NOS Nitric Oxide Synthase
Nrf2 Nuclear Factor Erythroid 2–Related Factor 2
NF-κB Nuclear Factor Kappa B
NOD Nucleotide-Binding Oligomerization Domain
OPC Oligodendrocyte Precursor Cell
PRKN Parkin
PD Parkinson's Disease
PAMP Pathogen-Associated Molecular Pattern
PRR Pattern Recognition Receptor
PNS Peripheral Nervous System
pMCAO Permanent Distal Middle Cerebral Artery Occlusion
PPARγ Peroxisome Proliferator-Activated Receptor Gamma
PI3K Phosphoinositide 3-Kinase
PARP1 Poly (ADP-Ribose) Polymerase-1
PET Positron Emission Tomography
PSEN Presenilin
PSP Progressive Supranuclear Palsy
PKB Protein Kinase B
PINK PTEN-induced Putative Kinase 1
REM Rapid Eye Movement
ROS Reactive Oxygen Species
RAGE Receptor For Advanced Glycation End Products
REM8 Receptor-Mediated Endocytosis 8

RBD REM Sleep Behaviour Disorder
RIG1 Retinoic Acid-Inducible Gene 1
RXR Retinoid X Receptor
RLH RIG1-Like Helicase
RLR RIG1-Like Receptor
HTRA2 Serine Protease
Sema3A Semaphorin-3A
SA-β-GAL Senescence-Associated Beta Galactosidase
SASP Senescence-Associated Secretory Phenotype
SNPs Single Nucleotide Polymorphisms
SPECT Single-photon Emission Tomography
SN Substantia Nigra
SNpc Substantia Nigra Pars Compacta
SOD Superoxide Dismutase
SOCS Suppressor of Cytokine Signaling Proteins
TLRs Toll-Like Receptors
TCM Traditional Chinese Medicine
TBI Traumatic Brain Injury
TCS Transcranial Sonography
TGF-β Transforming Growth Factor Beta
TUBB4B Tubulin Beta 4B Class IVb
TNF-α Tumor Necrosis Factor Alpha
TNFR1 Tumor Necrosis Factor Receptor 1
TH Tyrosine Hydroxylase
UCHL-1 Ubiquitin Carboxy-Terminal Hydrolase 1
UPR Unfolded Protein Response
VPS35 Vacuolar Protein Sorting 35
VCI Vascular Cognitive Impairment
VaD Vascular Dementia
VHM Venous Hypertensive Microangiopathy
WHO World Health Organization

List of Contributors

Abhishek Mishra	Department of Pharmacology, Post Graduate Institute of Medical Education & Research, Chandigarh-160012 (Punjab), India
Ambarish Kumar Sinha	Department of Clinical Research, School of Biosciences and Biomedical Engineering, Galgotias University, Greater Noida, Uttar Pradesh, India
Anil Kumar Singh	Department of Dravyguna, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005 (U.P.), India
Anindita Bhattacharjee	Neuroimaging Laboratory, School of Bio-Medical Engineering, Indian Institute of Technology, Banaras Hindu University, Varanasi-221005 (U.P.), India
Aparna Mishra	Department of Bioscience and Biotechnology, Banasthali Vidyapith University, Banasthali-304022 (Rajasthan), India
Archana Dwivedi	Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005 (U.P.), India
Ashutosh Kumar	Department of Pharmacology, Faculty of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005 (U.P.), India
Atul Kabra	School of Pharmacy, Raffles University, Neemrana, Alwar-301020 (Rajasthan), India
Bikash Medhi	Department of Pharmacology, Post Graduate Institute of Medical Education & Research, Chandigarh-160012 (Punjab), India
Bipin Maurya	Laboratory of Morphogenesis, Centre of Advance Study in Botany, Institute of Science, Banaras Hindu University, Varanasi-221005 (U.P.), India
Caridad Ivette Fernandez Verdecia	International Center of Neurological Restoration (CIREN), Basic Division, La Habana, Cuba
Chetan Keswani	Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi-221005 (U.P.), India
Christophe Hano	Laboratoire de Biologie des Ligneux et des Grandes Cultures, INRAUSC1328, Universitéd'Orléans, 45100 Orléans, France
Darshi Attanayake	Interdisciplinary Centre for Innovation in Biotechnology and Neurosciences, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Jayewardenepura Kotte, Sri Lanka
Deepika Joshi	Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005 (U.P.), India
Divya Raj Prasad	Department of Genetics and Plant Breeding, Institute of Agricultural Sciences, Banaras Hindu University, Varanasi-221005 (U.P.), India
Gaurav Kumar	Department of Clinical Research, School of Biosciences and Biomedical Engineering, Galgotias University, Greater Noida, Uttar Pradesh, India
Hagera Dilnashin	Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi-221005 (U.P.), India

Hardik Koria	Department of Pharmacology, Ramanbhai Patel College of Pharmacy, Charotar University of Science and Technology, Charusat Campus, Changa-388421, (Gujarat), India
Hareram Birla	Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi-221005 (U.P.), India
Héctor Eduardo López-Valdés	Departamento de Fisiología, Facultad de Medicina, Universidad Nacional Autónoma de México (UNAM), Ciudad de México, México
Hilda Martínez-Coria	Departamento de Fisiología, Facultad de Medicina, Universidad Nacional Autónoma de México (UNAM), Ciudad de México, México
Himanshu Verma	Department of Pharmaceutical Engineering and Technology, Indian Institute of Technology, Banaras Hindu University, Varanasi-221005 (U.P.), India
Kamal Uddin	Aligarh College of Pharmacy, Aligarh-202002 (U.P), India
K. Ranil D. de Silva	Interdisciplinary Centre for Innovation in Biotechnology and Neurosciences, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Jayewardenepura Kotte, Sri Lanka Institute for Combinatorial Advanced Research & Education (KDU-CARE), General Sir John Kotelawala Defence University, Colombo, Sri Lanka European Graduate School of Neuroscience, Maastricht University, Maastricht, The Netherlands
Lakmal Gonawala	Interdisciplinary Centre for Innovation in Biotechnology and Neurosciences, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Jayewardenepura Kotte, Sri Lanka European Graduate School of Neuroscience, Maastricht University, Maastricht, The Netherlands,
Nalaka Wijekoon	Interdisciplinary Centre for Innovation in Biotechnology and Neurosciences, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Jayewardenepura Kotte, Sri Lanka European Graduate School of Neuroscience, Maastricht University, Maastricht, The Netherlands
Natália Cruz-Martins	Faculty of Medicine, University of Porto, Porto, Portugal Institute for Research and Innovation in Health (i3S), University of Porto, Porto, Portugal, Institute of Research and Advanced Training in Health Sciences and Technologies (CESPU), Rua Central de Gandra, 1317, 4585-116 Gandra PRD, Portugal
Naveen Shivavedi	Shri Ram Group of Institutions, Faculty of Pharmacy, Jabalpur-482002 (M.P.), India
Nilay Solanki	Department of Pharmacology, Ramanbhai Patel College of Pharmacy, Charotar University of Science and Technology, Charusat Campus, Changa-388421 (Gujarat), India
Phulen Sarma	Department of Pharmacology, Post Graduate Institute of Medical Education & Research, Chandigarh-160012 (Punjab), India
Prasanta Kumar Nayak	Department of Pharmaceutical Engineering and Technology, Indian Institute of Technology, Banaras Hindu University, Varanasi-221005 (U.P.), India

Prasun Kumar Roy	Neuroimaging Laboratory, School of Bio-Medical Engineering, Indian Institute of Technology Banaras Hindu University, Varanasi-221005 (U.P.), India Centre for Tissue Engineering, Indian Institute of Technology, Banaras Hindu University, Varanasi-221005 (U.P.), India
Pratibha Thakur	Department of Bioscience, Endocrinology Unit, Barkatullah University, Bhopal- 462026 (M.P.), India
Pratistha Singh	Department of Dravyguna, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005 (U.P.), India
Raffaele Capasso	Universita Degli Studi di Napoli Federico II, Naples, Italy
Rohit Sharma	Department of Rasa Shastra and Bhaishjya Kalpana, Faculty of Ayurveda, IMS, Banaras Hindu University, Varanasi-221005 (U.P), India
Rubal Singla	Department of Pharmacology, Post Graduate Institute of Medical Education & Research, Chandigarh-160012 (Punjab), India
Ruchika Kabra	School of Pharmacy, Raffles University, Neemrana, Alwar-301020 (Rajasthan), India
Rupa Joshi	Department of Pharmacology, Post Graduate Institute of Medical Education & Research, Chandigarh-160012 (Punjab), India
Sarika Singh	Department of Neuroscience and Ageing Biology and Division of Toxicology and Experimental Medicine, CSIR-Central Drug Research Institute, Lucknow-226031, (U.P.), India
Shilpa Negi	Department of Neuroscience and Ageing Biology and Division of Toxicology and Experimental Medicine, CSIR-Central Drug Research Institute, Lucknow-226031, (U.P.), India
Sukala Prasad	Biochemistry & Molecular Biology Laboratory, Department of Zoology, Brain Research Centre, Banaras Hindu University, Varanasi-221001 (U.P.), India
Surya Pratap Singh	Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi-221005 (U.P.), India
Uttam Singh Baghel	Department of Pharmacy, University of Kota, Kota-324005 (Rajasthan), India
Vartika Gupta	Biochemistry & Molecular Biology Laboratory, Department of Zoology, Brain Research Centre, Banaras Hindu University, Varanasi-221005 (U.P.), India
Yoonus Imran	Interdisciplinary Centre for Innovation in Biotechnology and Neurosciences, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Jayewardenepura Kotte, Sri Lanka

CHAPTER 1

Globalizing Traditional Knowledge of Indian Medicine: Evidence-based Therapeutics

Hagera Dilnashin[1,*], Hareram Birla[1], Chetan Keswani[1] and **Surya Pratap Singh[1,*]**

[1] *Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi-221005 (U.P.), India*

Abstract: With the advent of modern medicine, the use of medicinal plants is an ancient therapeutic strategy used by traditional healers and is very useful in traditional medicine. Medicinal plants are compatible with human physiology, which has been adapted for centuries.

Keywords: Indopathy, Medicinal plants, Therapeutic strategy, Therapeutics, Traditional medicine.

INTRODUCTION

In today's scenario, scientists need to focus on finding the compounds of herbs involved in the cure, alleviation, and cure of the disease. Traditional medicine includes long-term treatments that people inherit and practice to prevent and treat illness. Plants have formed the basis of traditional medicinal systems. It consists of several medicinal systems from different parts of the world, which include Chinese herbal medicine (China), Indian herbal medicine (India), Kampo medicine (Japan), Native American medicine (US), Tibetan medicine (Tibetan), Jamu Genndong (Indonesia), traditional African medicine (Africa), and traditional Hawaiian medicine (Hawaii) [1, 2].

India has an ancient heritage of traditional medicine. *Materia medica* of India provides a wealth of information on the folklore practices and traditional aspects of therapeutically important natural products. Each of these traditional systems has unique aspects, but there is a common thread among their fundamental principles and practices in the use of natural products, mostly herbs [3 - 5].

[*] **Corresponding authors Hagera Dilnashin and Surya Pratap Singh:** Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi-221005 (U.P.), India; E-mails: hagera.dilnashin10@bhu.ac.in and suryasinghbhu16@gmail.com

Indopathy is a traditional Indian medicinal system that includes Ayurveda, Yoga, and Naturopathy, Unani, Siddha, and Homeopathy (AYUSH). It is a well-known medication system because of its various pharmacological effects that are beneficial to human health [6]. In addition to its strong neuroprotective potential, many studies have also described the significant therapeutic effects of herbal medicine against several central nervous system diseases [4, 7 - 9]. The biological effects of herbal plants have been generally attributed to ancient science's major protective effect. The results of studies with different mechanisms indicate the neuroprotective effects of plants, most of which mention positive effects on oxidative stress and other assessment parameters [5, 10 - 13]. The modulatory role of the alternative medicinal system will not only bring new drug discoveries [14] but also treat central nervous system diseases and help understand the complex pathophysiology of neurodegenerative diseases [3, 15 - 18].

CONCLUSION

Over time, Indopathy has been tested, and people have used it for their medical care for a long time. Before British rule, these were the main treatments in India but later changed under the influence of western culture. So Indopathy are well-rooted with a profound clinical basis, where scientific validation is sometimes the major constraint for their development. Despite these setbacks, Indopathy remains in India and continues to grow in the global market [19]. As the Western world pays more and more attention to herbal drugs, especially Indopathy, it is necessary to examine these systems and take appropriate measures to restore the concept of traditional medicine as the main therapeutic medicinal system [20, 21].

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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CHAPTER 2

Naturally-occurring Bioactive Molecules with Anti-Parkinson Disease Potential

Atul Kabra[1,*], Kamal Uddin[2], Rohit Sharma[3], Ruchika Kabra[1], Raffaele Capasso[4], Caridad Ivette Fernandez Verdecia[5], Christophe Hano[6,*], Natália Cruz-Martins[7,8,9,*] and **Uttam Singh Baghel[10,*]**

[1] *School of Pharmacy, Raffles University, Neemrana, Alwar-301020 (Rajasthan), India*

[2] *Aligarh College of Pharmacy, Aligarh-202002 (U.P), India*

[3] *Department of Rasa Shastra and Bhaishjya Kalpana, Faculty of Ayurveda, IMS, Banaras Hindu University, Varanasi, 221005 (U.P), India*

[4] *Universita Degli Studi di Napoli Federico II, Naples, Italy*

[5] *International Center of Neurological Restoration (CIREN), Basic Division, La Habana, Cuba*

[6] *Laboratoire de Biologie des Ligneux et des Grandes Cultures, INRAUSC 1328, Université d' Orléans, 45100 Orléans, France*

[7] *Faculty of Medicine, University of Porto, Porto, Portugal*

[8] *Institute for Research and Innovation in Health (i3S), University of Porto, Porto, Portugal*

[9] *Institute of Research and Advanced Training in Health Sciences and Technologies (CESPU), Rua Central de Gandra, 1317, 4585-116 Gandra PRD, Portugal*

[10] *Department of Pharmacy, University of Kota, Kota-324005 (Rajasthan), India*

Abstract: Parkinson's disease (PD) is a complex limiting neurodegenerative disorder, with a rising incidence. Current therapeutic options for PD have multiple limitations, and naturally occurring biomolecules, often known as phytochemicals, with potent neuroprotective activities, have been searched to meet the need. Thus, this chapter encompasses in-depth information on reported anti-PD activities of medicinal plants in light of available pre-clinical and clinical studies and shares the mechanisms of action proposed in fighting PD. Published information from PubMed, Scopus, Science Direct, Springer, Google Scholar, and other allied databases was analyzed. There is rising interest among researchers in investigating medicinal plants and their isolated compounds for their anti-PD efficacy. Scattered information about the anti-PD potential of *plants* and bioactive compounds is reported in the scientific domain. A total of 92 medicinal plants belonging to 63 families, exhibiting anti-PD activity were

[*] **Corresponding authors Atul Kabra, Christophe Hano, Natália Cruz-Martins & Uttam Singh Baghel:** School of Pharmacy, Raffles University, Neemrana, Alwar-301020 (Rajasthan), India, Laboratoire de Biologie des Ligneux et des Grandes Cultures, INRAUSC1328, Universitéd'Orléans, 45100 Orléans, France, Faculty of Medicine, University of Porto, Porto, Portugal & Department of Pharmacy, University of Kota, Kota-324005 (Rajasthan), India; E-mails: ruchika.p88@gmail.com, drusb1985@yahoo.com, ncmartins@med.up.pt & hano@univ-orleans.fr

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discussed. Botanical species have revealed an extreme potential, encouraging future examination. Data discussed here can be used for further research and clinical purposes.

Keywords: Bioactive molecules, Dopamine, Lewy bodies, Medicinal plant extracts, Parkinson's disease, Substantia nigra.

INTRODUCTION

Despite presenting a pathological mark of slowness, the manifestation and progression of Parkinson's Disease (PD) are insinuated [1], featured by the progressive loss of dopaminergic neurons in the pars compacta of substantia nigra and by the decline in dopamine levels in the basal ganglia striatum [2, 3]. Consequently, the cholinergic neurons' activity becomes comparatively dominant, while the nigrostriatal dopaminergic neuronal activity is decreased, which results in the advancement of movement disorder [4 - 6]. In the human system, PD is categorized by symptoms of motor neurons, *viz*. bradykinesia, resting tremors, rigidity, and postural instability [7], besides non-motor manifestations, such as neuropsychiatric abnormalities, disturbed sleep, dysautonomia, gastrointestinal disturbances, and sensory problems [8 - 12].

At the molecular level, although the pathophysiology of the disease still remains unclear, several pathways have been proposed to be involved in dopaminergic neuronal death, such as oxidative stress, mitochondrial injury, excitatory amino acid toxicity, ubiquitin-proteasome system damage, proteolytic stress, immune disorders, inflammatory reactions, dopamine transporter (DAT) inactivation, abnormal deposition of α-synuclein, and cell apoptosis through c-Abl activation [1, 13 - 15]. In this context, environmental factors, like permethrin pesticide exposure during brain development, have been associated with genetic and epigenetic changes leading to PD in rats, as well as in their untreated offspring (Fig. **1**) [16 - 19].

For several decades, the therapeutic gold standard for PD has been based on the use of levodopa, in combination with a peripheral decarboxylase inhibitor. However, the long-term use of these drugs often leads to multiple secondary effects, including gastrointestinal, respiratory, and neurological symptoms [20 - 22]. More recently, several drugs were approved by FDA for treating PD, but they also have various side effects, as summarized in Table **1** [23 - 27]. Hence, the search for natural products with anti-PD activity has largely increased in these years owing to their safer approach and cost-effectiveness. Though plentiful research has been carried out during the past decades on the anti-PD potential of

several botanical preparations, extracts, and isolated phytocompounds, only scattered information exploring their activity is accessible. Besides, earlier reports did not provide complete information apropos plant extract doses, animals used, and their possible anti-PD mechanism.

Considering this, the present chapter attempts to provide a comprehensive report on the anti-PD potential of several botanicals in light of available experimental and clinical studies.

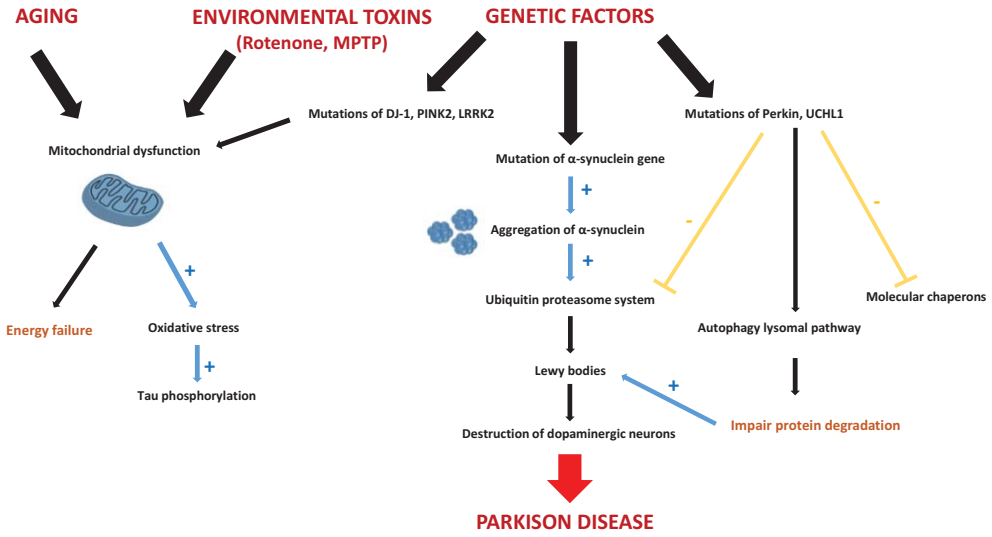

Fig. (1). Genetic, environmental, and lifestyle factors leading to PD.

Table 1. Recently FDA-approved anti-PD drugs.

S. No.	Drug	Brand Name	Mechanism of Action	Use	Side Effects	Approval Year	Company Name
1.	Safinamide	Xadago	MAO-B inhibitor	Adjunctive treatment to levodopa/carbidopa in patients with PD	Dyskinesia, fall, Nausea, Insomnia	2017	Newron Pharmaceuticals
2.	Amantadine	Gocovri	An uncompetitive antagonist of the NMDA receptor	PD dyskinesia	Hallucination, Dizziness, Dry Mouth, Peripheral Edema, Orthostatic, Hypotension	2017	Adamas Pharmaceuticals

CHAPTER 3

Indopathy for Neuroprotection in Parkinson's Disease

Archana Dwivedi[1] and **Deepika Joshi**[1,*]

[1] *Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005 (U.P.), India*

Abstract: Parkinson's disease (PD) is a chronic, multi-system, complex neurodegenerative disorder pathologically characterized by motor dysfunctions caused mainly due to the loss of dopamine (DA) neurotransmitters producing dopaminergic (DAergic) neurons. In Ayurveda, which is an indigenous medicine system of India, various medicinal herbs have been used for the treatment of PD since ancient times. A growing number of studies have proven that these Ayurvedic herbs can protect DAergic neurons from neuronal degeneration and hence can increase the level of DA. Phytochemicals or active ingredients present in these Ayurvedic herbs can target oxidative stress, mitochondrial dysfunction, neuroinflammation, apoptosis, and autophagy and can reduce α-synuclein (α-syn) protein aggregation, which are the basic pathological causes of neurodegeneration and can improve the motor ability and sometimes longevity in animal models of PD. The mainstay of treatment of PD is levodopa (L-Dopa), a precursor of DA, used for achieving the optimal level of DA. But its long-term use has debilitating side effects. Ayurvedic herbs have provided relief in PD with no or minimal side-effect even after long-term administration. Some plants, such as *M. pruriens,* are a natural source of L-Dopa. Here, we have discussed the major classes of phytochemicals found in Ayurvedic medicines and the pathogenic mechanisms of PD targeted by them. After that, we have discussed the recent advances in experimental and clinical data that support the neuroprotective properties of these phytochemicals used in Ayurveda and their potential to be developed as a therapeutic intervention for the prevention of PD.

Keywords: Ayurveda, *B. monnieri*, *C. Asiatica*, *C. Longa*, *C. sinensis*, *M. pruriens*, Neuroprotection, Parkinson's disease, Phytochemicals, *V. vinifera*, *W. somnifera*.

* **Corresponding author Deepika Joshi:** Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005 (U.P.), India; E-mail: drdeepikajoshi73@gmail.com

Surya Pratap Singh, Hagera Dilnashin, Hareram Birla & Chetan Keswani (Eds.)

INTRODUCTION

Parkinson's disease (PD) is the second most common and the major age-related neurodegenerative disorder affecting more than 10 million people worldwide, with an estimated annual incidence of 1.5 per 100,000 to 346 per 100,000 in different parts of the world and a prevalence of 41/100000 in the age of 40s to 1900/100000 in the age of 80s, equally affecting males and females [1 - 6]. It is a most common extrapyramidal neurodegenerative disorder primarily affecting voluntary movements and characterized by progressive degeneration of dopaminergic neurons in substantia nigra pars compacta (SNpc). The pathological hallmarks of PD manifesting due to DA deficiency are bradykinesia, rigidity, resting tremor, and postural instability [7]. PD also involves a broad range of non-motor symptoms, such as cognitive deficits, autonomic dysfunctions, and mood disorders [8]. Another important feature of PD is the abnormal aggregation of phosphorylated α-synuclein (α-syn) protein within Lewy bodies (LB). PD is a complex multifactorial disorder, and the exact etiology of PD is not yet clear. The following are considered risk factors for the development of PD- genetic factors, aging, environmental toxins, drugs, infections, and ethnicity. Many of the pathogenic processes in PD are in parallel to aging shifts [2, 9 - 12].

Pharmacological treatment of PD can be accomplished with L-Dopa, DA agonists, catechol-O-Methyl transferase (COMT) inhibitors, monoamino oxidase-B (MAO-B) inhibitors, antimuscarinics, or amantadine. The mainstay of treatment and the most effective symptomatic therapy remains the use of dopamine precursor L-Dopa [13]. Other strategies of PD treatment are deep brain stimulation and stem cell transplantation into the striatum [14]. Although there is no cure for PD presently, attempts to slow or stop the neuronal cell loss in the disease have failed [15]. Also, with the advancement of disease duration, the effectiveness in relieving symptoms reduces, so higher doses of L-Dopa are required, leading to the development of drug-induced motor complications [16 - 19].

Ayurveda (Ayu: life, the combined state of body, senses, mind, and soul; Veda: science. Ayurveda: the science of life, Sanskrit) is an ancient Indian medical system and is the oldest functional science-based system of medicine in the world. There are three dynamic principles of humor according to Ayurveda, namely, “doshas”, “dhatus”, and “malas”. “Doshas” governs the body’s physiological and physicochemical activities. It can be of three types, namely, “Vata” (responsible for movement), “Pitta” (responsible for transformation), and “Kapha” (responsible for anabolic activities). In Ayurveda, Physiology is the situation of harmony in the functioning of these “Doshas”, and pathology is the situation of the discordance in their functions affecting the “Dhatu” (structural element) and

the "Mala" (elimination of wastes). So "Vata doshas" is responsible for all the movements and sensations, including motor actions [20, 21].

In Ayurvedic literature, Paralysis agitans/ PD are called "Kampa Vata" (Kampa: tremor). "Charaka Samhita", "Madhavanidana" and other Ayurvedic literature contain and describe various signs and symptoms of "Kampa Vata", such as no inclination for movement (akinesia), drooling of saliva, love of solitude (depression), constant drowsy feeling, and fixation and whiteness of eyes (probable reptilian stare), "Pravepana" (excessive tremor), "Sirahkampa" (skull tremor), "Cestapranasa" (loss of movement), "Stabdhagatratva" (stiffness of the body), and "Anukirna svara" (stammering), "Cittanasa" (loss of mind or dementia), "Buddhi pramaha" (Mental confusion) [21]. Ayurveda stresses an inherently holistic approach to health and disease, and treatment is focused on modifying the pathophysiology of the disease and symptom management.

This Ayurvedic health management system may be complementary or alternative to the existing medical system being used, especially in the case of chronic conditions. A number of plants with therapeutic benefits are used in Ayurveda for the treatment of neurodegenerative diseases. These Ayurvedic medicines are used as concoctions or concentrated plant extracts without isolation of active compounds or after the isolation and purification of one or two active compounds. But sometimes, the isolation of the "active compound" has made the compound ineffective. Therefore, while using the plant-based drug, one must start with a combinatorial approach when evaluating candidate compounds. A reverse pharmacology approach, based on traditional medicine as Ayurveda, can be exploited as a smart strategy for discovering new drug candidates and also for the development of better synergistic herbal formulations with enhanced performance in terms of safety, efficacy, and cost [16, 17, 22 - 24]. These pharmacological approaches involving herbal extracts from medicinal plants or nutraceuticals have been shown to impart at least three clinical beneficial effects for better management of PD:

a. Affecting the neurodegenerative process from the prodromal stage onward.
b. Reducing the incidence and severity of the side effects of the conventional therapy.
c. Improving non-motor symptoms [25].

CHAPTER 4

Neuroprotective Sri Lankan Plants: Back to the Future with Phytomedicine

Nalaka Wijekoon[1,3], Yoonus Imran[1], Darshi Attanayake[1], Lakmal Gonawala[1,3] and **K. Ranil D. de Silva[1,2,3,*]**

[1] *Interdisciplinary Centre for Innovation in Biotechnology and Neurosciences, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Jayewardenepura Kotte, Sri Lanka*

[2] *Institute for Combinatorial Advanced Research & Education (KDU-CARE), General Sir John Kotelawala Defence University, Colombo, Sri Lanka*

[3] *European Graduate School of Neuroscience, Maastricht University, Maastricht, The Netherlands*

Abstract: Sri Lanka is listed as the top 34th biodiversity hotspot globally and has the highest biodiversity per unit area of terrestrial in the Asian continent. Intriguingly, it has been reported that 3771 flowering plant species are grown in Sri Lanka, of which 927 (24%) are endemic to the country, and 1430 species are considered medicinal plants. Surprisingly, it is reported that up to 40% of all new molecular entities submitted to the Food and Drug Administration (FDA) approval are either natural products or natural product-derived compounds. This chapter aims to explore the therapeutic potential of Sri Lankan plants/natural products in neuroprotection as possible synergistic targets of the nuclear factor erythroid (NF-E2)-related factor 2 (Nrf2) pathway. Nonetheless, the symptoms of neurological diseases are different; oxidative stress plays a central role in pathogenesis, thus, Nrf2 activation will counteract common pathogenic processes involved in neurodegener-ative/neuro-muscular disorders. Therefore, targeting Nrf2 signaling may provide a therapeutic option to delay onset, slow progression, and ameliorate symptoms of neurological disorders. However, when translating from the bench to the bedside, the knowledge of the timing of Nrf2 modulating compounds and dosage is crucial to define at which point should an Nrf2 activator be used versus an Nrf2 inhibitor. In this scenario, blends of natural products that synergize and provide multi-site action on Nrf2 regulation *via* different pathways are vital and will pave the way for the development of evidence-based effective neuro-nutraceuticals with a stride of innovation.

Keywords: Inhibitors, Keap1, Neurological disorders, Nrf2, PKC pathway.

* **Corresponding author K. Ranil D. de Silva:** Interdisciplinary Centre for Innovation in Biotechnology and Neurosciences, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Jayawardenepura Kotte, Sri Lanka; Institute for Combinatorial
Advanced Research & Education (KDU-CARE), General Sir John Kotelawala Defence University, Colombo, Sri Lanka & European Graduate School of Neuroscience, Maastricht University, Maastricht, The Netherlands; E-mails: ranildesilva@kdu.ac.lk and ranil@sjp.ac.lk

Surya Pratap Singh, Hagera Dilnashin, Hareram Birla & Chetan Keswani (Eds.)

INTRODUCTION

"Genetic error led humans to evolve bigger, but more vulnerable, brains", *Horizon; The EU Research And Innovation Magazine, 2018* [1].

The human brain is considered an "expensive tissue" that consumes an outstanding 20% of the total body energy budget despite the brain representing only 2% of body mass. Enhancing the brain activity and its functions was top in the research priorities, thus neuroprotection was among the forgotten and forsaken topics in the past. However, this trend has changed in the 21st century, with the argument that increased longevity is an opportunity or a threat to the stability of societies. The answer depends not only on whether populations are living longer but whether they are experiencing the negative health effects of aging [2 - 5].

"*Let food be thy medicine and medicine be thy food*", the popular quote by Hippocrates (400 BC), was further supported by Ibnu Sina or Avicenna, a Persian physician (981–1037 BCE), who stated that 'attention to the prevention of diseases rather than their treatment', which is an unmet need of current era of medicine [6 - 8]. The idea of "You are what you eat" was not novel to the 3 millennia-old indigenous medicinal systems in Sri Lanka, which are still in use and generally the first approach for disease control by the locals [9 - 11].

Typically, the herbs used for medicinal purposes are evergreen in nature, grown in the backyards of houses, and sometimes considered weeds. The traditional Sri Lankan education system centered on the temple, and the knowledge passed down by the ancestors made most Sri Lankans familiar and were even able to identify or administer the herbs growing within their area of residence even without the advice of a traditional medicinal practitioner [12, 13]. Sri Lanka was listed as the top 34th biodiversity hotspot globally and it has the highest biodiversity per unit area of terrestrial in the Asian continent [13]. Sri Lanka is gifted with many plant resources. It has been reported that there are 3771 flowering plant species grown in Sri Lanka. Out of them, about 927 (24%) are endemic to the country. Also, 1430 species are considered to have medicinal value. Of these medicinal plants, 174 (12%) are endemic to Sri Lanka. Also, it is reported that around 250 species are commonly used in traditional medicine [9, 14].

Nonetheless, the scientific explanation of the curative powers remained unsolved; natural products based on traditional remedies have been employed for thousands of years [15 - 19]. These time-tested natural remedies have long served as a chemical matter for the discovery and/or development of modern pharmaceuticals. Surprisingly, it is reported that up to 40% of all new molecular entities submitted to the Food and Drug Administration (FDA) approval are either

natural products or natural product-derived compounds [18, 20 - 30]. The scientific identification of possible targets to natural products intriguingly has usually paved the way for new biology or opened entirely novel fields. This is the case for the nuclear factor erythroid (NF-E2)-related factor 2 (Nrf2) pathway and its relationship with natural products [21, 31 - 38].

NRF2 AS A POTENTIAL THERAPEUTIC TARGET

The Nrf2/ARE pathway is modulated by the Kelch-like ECH-associated protein 1 (Keap1). In basal conditions, Keap1 protein acts as an Nrf2 repressor, binding to Nrf2 and maintaining it in the cell cytoplasm [39 - 42]. Keap1 regulatory protein also directs Nrf2 to ubiquitination and degradation by proteasomes, thereby limiting its basal cellular levels [43, 44]. Considering that the Nrf2 signaling pathway can regulate at least 600 genes, of which 200 encode cytoprotective proteins involved in diseases and the dynamic connections between diseases and drugs, modulating Nrf2 activity is a promising pharmacological approach [45 - 48]. A central theme emerging from the identification of these target genes and their functions is resistance to oxidants and electrophiles. Notably, three major groups of Nrf2 target genes regulate drug metabolism and disposition, antioxidant defense, and oxidant signaling, respectively, to impact the response to oxidants and electrophiles (Fig. **1**). In addition, Nrf2 regulates proteasomal protein degradation [49, 50], cell proliferation [51 - 54] and metabolic reprogramming as well [55 - 63].

Nrf2 is ubiquitously expressed [64 - 66] and, in the brain, is an important defense against toxic insults in both glial cells as well as neurons [67 - 69]. In addition to upregulating numerous antioxidant enzymes, Nrf2 can also increase the expression of anti-inflammatory mediators, phase I and II drug-metabolizing enzymes as well as mitochondrial pathways [70 - 79].

NRF2 IN AGING/ NEURODEGENERATIVE DISORDERS

Developing a detailed understanding of the brain, which is commonly referred to as “the final frontier of science”, is still in its relative infancy, but there are already several key observations that clearly attest to the power of the mind for proper coordination [80, 81]. Although ND has distinct pathologic features, there is considerable evidence to support oxidative stress as a common pathogenetic mechanism. Evidence of lipid peroxidation, protein nitration, and nucleic acid oxidation is abundant in affected brain regions of ND [82 - 84].

CHAPTER 5

Phytochemicals from Indian Medicinal Herbs in the Treatment of Neurodegenerative Disorders

Himanshu Verma[1], Naveen Shivavedi[2] and **Prasanta Kumar Nayak[1,*]**

[1] *Department of Pharmaceutical Engineering and Technology, Indian Institute of Technology, Banaras Hindu University, Varanasi, 221005 (U.P.), India*

[2] *Shri Ram Group of Institutions, Faculty of Pharmacy, Jabalpur-482002 (M.P.), India*

Abstract: Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic lateral sclerosis are the major cause of disability and mortality. These disorders are appearing in the current era due to aging and stress-full lifestyles. For the treatments of these disorders, several conventional drugs are available but due to higher cost and dangerous adverse effects. Therefore, scientists are focusing more on medicinal herbs containing phytochemicals because these medicinal herbs are more effective, low cost, and show less harmful side effects to cure neurodegenerative disorders. Indian medicinal herbs are the most effective medicines and indigenous to India. Since ancient times, medicinal herbs have been used for treating neurodegenerative disorders. Indian medicinal herbs containing phytochemicals possess beneficial therapeutic effects for the treatment of neurodegenerative disorders, majorly having various compounds such as alkaloids, sesquiterpenes, triterpenoids, polyphenols, flavonoids, saponins, and essential oils which show anti-inflammatory and anti-oxidative properties. In this chapter, we highlighted and discussed the importance of some Indian medicinal herbs, such as *Bacopa monnieri* (Brahmi), *Centella asiatica*, *Curcuma longa* (turmeric), *Allium sativum* (garlic), *Terminalia chebula* (haritaki), *Celastrus paniculatus* (Jyotishmati), *Glycyrrhiza glabra* (Licorice), and *Acorus calamus* (Vacha) containing phytochemicals with their mechanism of action on neurodegenerative disorders.

Keywords: Alzheimer's disease, Flavonoids, Huntington's disease, Parkinson's disease, Phytochemicals, Polyphenols.

INTRODUCTION

Neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Amyotrophic lateral sclerosis

* **Corresponding author Prasanta Kumar Nayak:** Department of Pharmaceutical Engineering and Technology, Indian Institute of Technology, Banaras Hindu University, Varanasi, 221005 (U.P.), India; E-mail: pknayak.phe@iitbhu.ac.in

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(ALS) occurred due to degeneration of neurons or neuronal damage. Neuroprotection is the strategies and mechanisms used against neuronal damage to treat neurodegenerative disorders [1]. Degeneration of neuronal cells and protein aggregation are the major factors involved in neuropathological and brain aging [1 - 3]. Neurodegenerative disorders are the main cause of morbidity and mortality with cognitive impairment in elderly people [4]. Etiologically, aging is the primary risk factor for neurodegeneration [5, 6]. Growing populations day by day and average life span increase the prevalence and incidences of neurodegenerative diseases [4]. Epidemiologically, these diseases are the second leading cause of death worldwide among elderly people by the 2040s, and the global aging population may rise by 2050 to 2 billion people [7 - 13].

AD is the first and most common type of dementia characterized by the accumulation of amyloid and hyper-phosphorylated tau protein in the brain, which is marked by progressive memory loss in elderly people [14]. PD is another common neurodegenerative disorder (movement disorder), and the etiology of PD is unclear, but several genetic and environmental causes have been identified [15]. HD is a common genetic disorder of autosomal dominant inheritance. In HD, degeneration of medium spiny neurons due to trinucleotide repeat expansion (CAG), causes continuous involuntary motor movements [16]. Amyotrophic lateral sclerosis is an adult-onset neurodegenerative disease characterized by the accumulation of ubiquitinated protein that occurs due to the loss of motor neurons in the central nervous system, leading to muscle atrophy and respiratory failure [17, 18].

However, several categories of synthetics drugs are available for the management of neurodegenerative disorders, such as cholinesterase inhibitors, N-methyl-D-aspartic acid receptor antagonists, dopamine agonists, catechol-o-methy-ltransferase inhibitors, anticholinergic drugs, dopamine decarboxylase inhibitors, monoamine oxidase inhibitors, tetrabenazine, edaravone, riluzole, *etc.* All these conventional drugs have therapeutic benefits but contain some unwanted dangerous side effects, such as psychosis, depression, low blood pressure, dry mouth, drowsiness, anxiety, difficulty with balance, *etc*.., that may harm the patients [19]. Therefore, treatment with Indian medicinal herbs got more significant as it may have potential anti-oxidative and anti-inflammatory effects, which can be safer than conventional drugs. These phytochemicals are well-accepted treatments that can modulate neuronal function and protective mechanisms against several neurodegenerative disorders [20 - 25].

Since ancient times, medicinal herbs have been used in India to treat neurodegenerative disorders. Here, we are discussing some novel studies and mechanisms of Indian medicinal herbs such as *Bacopa monnieri*, *Centella*

asiatica, *Curcuma longa*, *Allium sativum*, *Terminalia chebula*, *Celastrus paniculatus*, *Glycyrrhiza glabra*, and *Acorus calamus* that may treat neuro-degenerative disorders without any harmful effects (Fig. **1**).

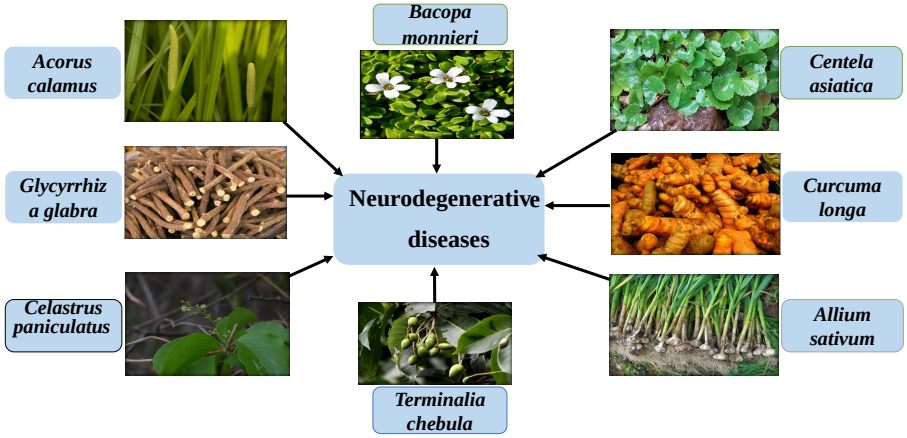

Fig. (1). Indian medicinal herbs used in the treatment of neurodegenerative disorders.

B. MONNIERI

B. monnieri (Brahmi, family: *Scrophulariaceae*) is a phytochemical found throughout the Indian subcontinents, as a most traditional herb in 'Ayurvedic Materia Medica' and used against mental disorders such as anti-anxiety, anti-epileptic, memory enhancer, tranquilizer, anti-oxidant and anti-inflammatory agent [26 - 31].

Phytoconstituents of *B. monnieri*

Triterpenoid saponins are the major constituents of *B. monnieri* called jujubacogenin, psudojubacogenin, and bacosides glycosides moieties [32]. There are several classes of saponins identified from I to XIII, and bacosides are the well-known constituents for pharmacological action [33]. Bacosides A and B, and D-mannitol play an important role in neuroprotection [34] (Table **1**).

Neuroprotective Activity of *B. monnieri*

In a clinical study, *B. monnieri* standardized extract (300 mg; orally) twice a day was used for 6 months, resulting in improved cognitive function in AD patients [35]. Numerous researches suggested that bacosides (*B. monnieri* components) work against oxidative stress and cognitive deterioration with different mechanisms of action and improve memory and the ability to learn in rodents [36 - 40]. More studies stated that "Brahmi" reduces reactive oxygen species (ROS), neuroinflammation, aggregation inhibition of amyloid-β, and better cognitive and

CHAPTER 6

Neuroprotective Alkaloids: Neuromodulatory Action on Neurotransmitter Pathway

Pratibha Thakur[1,*]

[1] *Department of Bioscience, Endocrinology Unit, Barkatullah University, Bhopal- 462026 (M.P.), India*

Abstract: Equilibrium in excitatory and inhibitory neurotransmitter signal transmission is necessary for the proper functioning of the brain, and alteration can stimulate the negative feedback mechanism that causes various neuropathogenesis. Disturbances like oxidative stress and alteration in the metabolism of neurotransmitters like γ-aminobutyric acid (GABA), acetylcholine (Ach), serotonin, dopamine, and glutamate, are important factors for the progression of neurodegenerative disorder (NDDs). Plant alkaloids have the potential to modulate the neurotransmitter signal transmission in the central nervous system and can provide a better alternative to the synthetic molecule. In the present chapter, we summarize the potential efficacy of plant alkaloids *via* functioning as anti-oxidant, monoamine oxidase (MAO) inhibitor, glutamate receptors-N-methyl-D-aspartate (NMDA) antagonist, acetylcholinesterase (AcHE) inhibitor and shows potential therapeutic effects against NDDs.

Keywords: Alkaloids, Central nervous system, Neurodegenerative disorder, Neurotransmitter.

INTRODUCTION

Different conditions affecting the nervous system, and nerve cells due to degeneration in the structure and functioning of the nervous system, are described under the superordinate phrase "neurodegenerative diseases" (NDDs). Studies from different clinical and experimental investigations showed that the alteration in physical and chemical properties of protein results in aggregation of these proteins and consequently degeneration in the structure and function of neurons [1 - 7]. The main symptoms of the NDDs are problems with movement (ataxia) or mental functioning (dementia), or both, causing morbidity and fatality. The most common neuropsychiatric and neurological disorders are schizophrenia, anxiety, depression, Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's

* **Corresponding author Pratibha Thakur:** Department of Bioscience, Endocrinology Unit, Barkatullah University, Bhopal- 462026 (M.P.), India; E-mail: pratibha000136@gmail.com

Surya Pratap Singh, Hagera Dilnashin, Hareram Birla & Chetan Keswani (Eds.)

disease (PD), Amyotrophic lateral sclerosis (ALS), spinocerebellar ataxia (SCA), spinal muscular atrophy (SMA) and seizure disorder [8]. The available treatment for these diseases gives only symptomatic relief to the patient, therefore, there is a need to explore actual treatment. Since prehistoric times, herbal medicine has been used in traditional systems by different cultures throughout the world. As per the world health organization (WHO) recommendation, any plant which contains a bioactive component with medicinal properties can be used directly or indirectly to cure the disease as well as drug synthesis and design [9]. The traditional system of herbal medicine is still being used for the treatment of many diseases, especially in the rural area, and is in high demand due to various factors like the high cost of modern medicine, inadequate supply of drugs, rise in population, and side effects of synthetic drugs. 50% of modern medicines are derived from plants, and approximately 391,000 species of plants are present on earth, but only limited have been highlighted with medicinal properties [10]. In the past decades, researchers have focused on the continuous failure of synthetic drugs in various clinical trials [11 - 16]. A medicinal plant contains different chemical compositions, including alkaloids, phenolics, flavonoids, terpenoids, steroids, saponins, and glycosides with a broad range of biological activities like anti-oxidative, anti-carcinogenic, anti-bacterial, anti-thrombotic, anti-inflammatory, and regulate blood pressure, blood cholesterol, and blood sugar concentration [17 - 19]. The multiple components of herbal medicines and multiple targeting natures of NDDs suggest that herbal medicines may achieve an effective clinical outcome by dealing with the complex mechanism of NDDs. Among many functions, bioactive plant compound shows positive effects on the central nervous system by neuromodulatory action on some neurotransmitter [20 - 25]. Studies from the clinical and non-clinical investigation showed that some NDDs, and mood affective disorders like AD, and PD are caused by an alteration in glutamate, γ-aminobutyric acid (GABA), or acetylcholine (Ach) [20, 21, 26, 27]. Along with this, Ach is also responsible for the cholinergic signaling in the central nervous system (CNS), as well as associated with β-amyloid (Aβ) plaque distribution in the brain [28]. There are a number of bioactive compounds of plants with neuroprotective properties, and alkaloids are one of them with antidepressant properties by dopaminergic agonists and inhibition of the acetylcholinesterase (AChE), monoamine oxidase (MAO), and glutamate toxicity [8, 20, 29].

SOURCE STRUCTURE AND CLASSIFICATION OF ALKALOIDS

Alkaloids are one of the important groups of phytoconstituents containing carbon, hydrogen, nitrogen, and oxygen and naturally occur in plants [20]. The nitrogen present in the alkaloid molecule ring system causes the alkalinity of these compounds and is classified into different classes like indoles, quinolines, isoquinolines, pyridines, pyrrolidines, pyrrolizidines, steroids, tropanes, and

terpenoids. Alkaloids are also classified on the basis of the family of plant species in which they occur, like opium alkaloids present in the opium poppy (*Papaver somniferum*) [30]. In pure form, alkaloids are colorless, odorless, and crystalline solid, and to date, more than 3000 alkaloids have been explored in over different 4000 plant species. Furthermore, the study showed that several families of plants like Solanaceae, Ranunculaceae, Papaveraceae, and Amaryllidaceae are rich in different types of alkaloids [31].

Alkaloids show various pharmacological potential in modern medicine, such as anti-hyperglycemic, analgesic, anticancer, antibacterial, and antiarrhythmic, but are only specifically used in modern medicine [32]. Along with this, some alkaloids like cocaine, caffeine, and nicotine show stimulant effect in CNS, and psilocin exhibits a psychotropic effect. Alkaloids show different neuroprotective properties against NDDs through inhibition of AChE enzyme kinetics [33], the elevation of inhibitory neurotransmitters, *i.e*., GABA [33], and much more, as described in Table **1**.

Table 1. Different classes of alkaloids and effective in neurodegenerative disorders.

Alkaloid	Class	Source	Mechanism	Disease	Refs.
Aporphine alkaloids	Nantenine	*Nandina domestica*	Inhibit the Ca^{2+} influx AcHE Inhibitor	Epilepsy AD	[34, 35]
Isoquinoline alkaloids	Galantamine	*Galanthus nivalis Leucojum aestivum Galanthus woronovii*	AcHE Inhibitor, allosteric modulation of nicotinic Ach receptor	PD	[36]
	Berberine	*Berberis aristata Berberis aquifolium Hydrastis canadensis Coptis chinensis*	AcHE inhibitor, NMDA inhibitor, up-regulation of autophagic function	Epilepsy HD, PD, AD	[37]
	Salsoline	*Salsola oppositefolia*	AcHE inhibitor	AD	[38]
	Morphine	*Papaver somniferum*	Anti-oxidant, increase GABA	AD	[31, 39]
	Montanine	*Hippeastrum* vittatum	AcHE inhibitor	AD, Epilepsy	[40]
Indole Alkaloids	Geissospermine	*Geissospermum vellosii*	AcHE inhibitor	AD	[41 - 44]

CHAPTER 7

South Indian Medicinal Herb: An Extensive Comparison of the Neuroprotective Activity

Pratistha Singh[1,*], Ashutosh Kumar[2,*] and **Anil Kumar Singh[1]**

[1] *Department of Dravyguna, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005 (U.P.), India*

[2] *Department of Pharmacology, Faculty of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005 (U.P.), India*

Abstract: Medicinal Plants have secondary metabolites containing various phytoconstituents. Traditionally, medicinal plants are used in several diseases like cancer, diabetes, neurodegenerative disorder, *etc*. Flavonoids, Tannin, Phenols, Phenylpropanoids, Isoprenoids, and alkaloids are present in several medicinal plants, which play a very important role to promote health benefits and defensiveness for other disorders. Neurological disorders are prone to the elderly and difficult to treat. Several medicinal plants have been recognized as beneficial in neurological disorders. Various types of plant extract and formulations are present in ancient texts, which are effective in such disorders and should be explored scientifically to mitigate neurodegenerative disorders. In this chapter, we will focus on South Indian medicinal plants which are effective in neurological disorders or have neuroprotective properties.

Keywords: Anti-oxidant, Medicinal plants, Neuroprotective activity, Secondary metabolites, South India.

INTRODUCTION

Chronic neurodegenerative disorders such as Parkinson's disease (PD), and Alzheimer's disease (AD), occur due to unable to defend the central nervous system against any type of neural injury. Neuroinflammation has been concerned with the pathogenesis of several neurodegenerative diseases such as AD, PD, and multiple sclerosis (MS) [1]. Herbal medicine has precious resources in mitigating and prophylaxis several CNS disorders and helps improve health. Increasing irregularity in normal life leads to several disorders in the human body. In allopa-

[*] **Corresponding authors Pratistha Singh & Ashutosh Kumar:** Department of Dravyguna, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005 (U.P.), India & Department of Pharmacology, Faculty of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi221005 (U.P.), India; E-mails: psingh30.bhu@gmail.com & ashusingh1612@gmail.com

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ths, several medicines and surgery methods are present which are effective but do not cure permanently. Herbal products contain complex mixtures or formulations of bioactive compounds such phytochemicals, phenylpropanoids, isoprenoids and alkaloids, and saponin, which are responsible for biological activity [2]. Medicinal plant extract has become the most common supplement to prevent several neural disorders. The standardized extract of several medicinal plants is effective in the local area; it should be explored on a global level. Developing countries depend on traditional medicine, such as plant products and formulations for primary health, as estimated by WHO [3]. India is full of biodiversity, and 12 major biodiversity regions are present in the Southern part of India and blessed with a huge number of medicinal plants, including two major biodiversity zone, Western Ghat and Eastern Ghat. It is reported that approximately 2000 medical species are present in Western Ghat. The majority of plant species are limited to the southern isthmus [4]. In the present study, we described medicinal plants and their phytoconstituents as neuroprotective medicine (Fig. **1**). We briefly discussed neurodegenerative diseases, AD and PD in particular, with emphasis on the preventive strategies represented by herbal medicine [5 - 10]. We provide an ethnobiological approach, focusing on medicinal herbs used by different traditional medicines and their neuroprotective components.

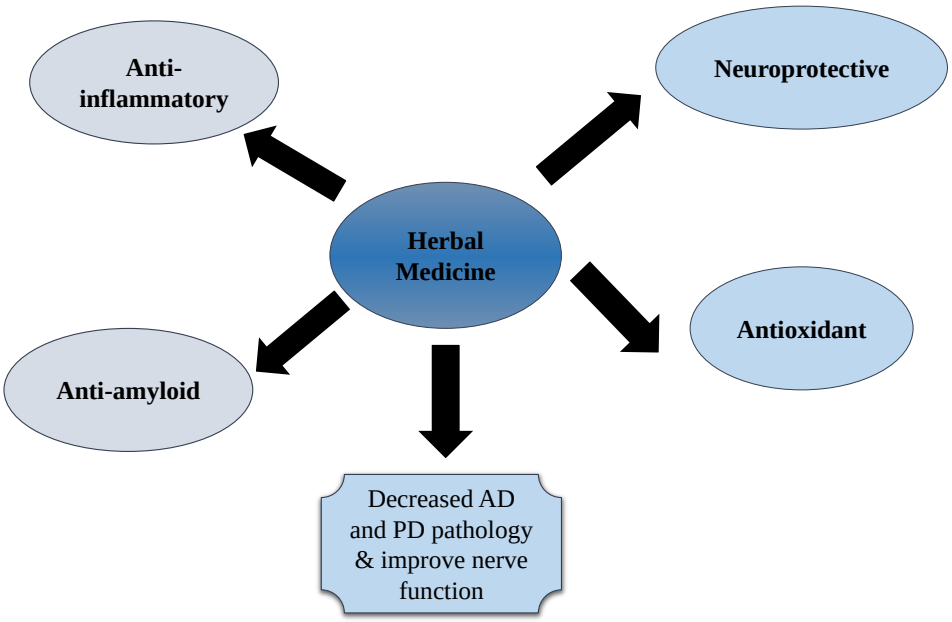

Fig. (1). Effects of plant secondary metabolites present in herbal medicine; Anti-inflammatory, neuroprotective, anti-amyloid, and anti-oxidant activities. It is effective in the inhibition of the formation of amyloid plaques in neurological disorders, inhibition of reactive oxygen species, and prevent inflammatory.

NEURODEGENERATIVE DISEASE

Neurodegeneration is a process that leads to damage of neurons and also loss of the function and structure of neurons. This result leads to impaired cognition and neurological disorder leading to PD, AD, dementia, epilepsy, and cerebral ischemia.

AD is an accumulation of beta-amyloid plaques between nerve cells (Neurons) present in the brain. It is a common form of dementia in adults and is an unalterable degeneration of the brain that causes an interruption in memory and other neural function. It causes many other troubles such as confusion, visual complication, agitation, poor judgment, and hallucination and may lead to neuron death. Genetic and environmental factors are also responsible for the disease, such as diet, smoking, brain injury, diabetes, and other medical conditions [11].

PD was first described by James Parkinson. It is the second most common neurodegenerative disease. Young children and people mostly over 50-60 years are most affected [12]. PD is characterized by the loss of 50-70% of dopaminergic neurons in the substantia nigra (SN), which results in a fall in dopamine levels in the brain. PD causes several abnormalities in the body: slow movements (Bradykinesia) and muscle rigidity [13 - 16]. Several other abnormalities are seen in PD: cramped handwriting, expressionlessness, difficulty swallowing, and mitochondrial dysfunction. Genetic and Reactive oxygen species generation causes such types of neurodegenerative diseases [17 - 21].

MEDICINAL PLANTS

Avicennia marina forssk. Vierh

A. marina, commonly known as grey mangrove or white mangrove, belongs to the Acanthaceae family. It is found in Kerala and Tamil Nadu region in South India. The plant is a rich source of phytocompounds such as alkaloids, aromatic lipids, phenylethanoid glycosides (PGs), and other effective compounds. It has pharmacological activities such as anti-microbial activity [22]. Marinoid J was obtained from fruits of *A. marina* that significantly improve cognitive deficits in vascular dementia (VD) rats model, regulate a set of proteins that affect oxidative stress and apoptosis, and decrease oxidative stress, and apoptosis of hippocampal CA1 neurons. Marinoid J shows a novel opening treatment of VD [23].

CHAPTER 8

Therapeutic Anti-Parkinson's Role of *Bacopa monnieri* and Reconsideration of Underlying Mechanisms

Vartika Gupta[1] and **Sukala Prasad**[1,*]

[1] *Biochemistry & Molecular Biology Laboratory, Department of Zoology, Brain Research Centre, Banaras Hindu University, Varanasi-221005 (U.P.), India*

Abstract: Neurodegeneration leads to several life-threatening brain disorders such as Parkinson's disease, Alzheimer's disease, and many more. Such kinds of diseases have a great impact on normal life patterning and may cause other severe symptoms, which are sometimes incurable. PD is the second most common disease characterized by the symptoms like Bradykinesia, resting tremor, postural instability, and some motor symptoms involving cognitive impairment and sleep disturbance. Memory plays a major role in sustaining the life of an individual. The development of an advanced molecular technique for treating PD increases day by day, but the complications in these techniques also cannot be ignored, so scientists move towards ayurvedic herbs to treat such kinds of disorders. *Bacopa monneiri* is an ayurvedic medicinal creeping plant used since ancient times to treat several kinds of diseases, including brain diseases. It has many components which are useful in neuroprotection and ameliorating PD. The core aim of the present chapter is to summarize and discuss how *B. monnieri* plays a therapeutic role in PD

Keywords: Alpha-synuclein, Antioxidant, *B. monneiri*, Nootropic herb, Oxidative stress, Parkinson's disease.

INTRODUCTION

The brain is the most important and complex organ of the body, which serves to control and coordinate the mental and physical activity of humans and other vertebrates. It consists of millions of neuronal cells, and each neuronal cell is connected to itself *via* a synapse. Synapse acts as a junction between two nerve cells, passing the impulse by diffusion of neurotransmitters [1, 2]. These neurons act in coordination with each other to acquire new information and store them for

* **Corresponding author Sukala Prasad:** Biochemistry & Molecular Biology Laboratory, Department of Zoology, Brain Research Centre, Banaras Hindu University, Varanasi-221005 (U.P.), India; E-mail: s.sprasadbhu@gmail.com

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future use, and this ability of the brain is known as learning and memory. Conversely, learning is the process of acquisition of new information or experiences, and storing the learned information for later use is termed as memory, both of which are complex and major functions of the brain [3]. The molecular mechanism of learning and memory is governed by synaptic plasticity, which is the ability of neurons to strengthen and weaken in response to an increase and decrease in the given signals [4]. In short, the brain is the master controller of the body and a very complex organ that learns and forms memory with the help of neurons which can be retrieved for later use.

However, sometimes, the brain also loses its ability to do all these functions due to disturbance in their neurophysiological process which leads to several kinds of neurodegenerative disorders such as Alzheimer's disease [AD], Parkinson's disease [PD], Huntington's disease [HD] and undergo other neuropathological conditions like brain injury, aging, metabolic disorders, and neuropsychiatric problems. AD and PD are the first and second most common neurogenerative diseases, respectively. The key difference lies in their onset period, associated key protein, memory, cognition, personality, more prominent movement, *etc*. [5]. PD is an age-related neurodegenerative disorder characterized by motor impairment involving rigidity, bradykinesia, rest tremor, and postural instability, along with non-motor complications, such as autonomic dysfunctions, cognitive neuropsychiatric changes, and sleep disturbances [6, 7]. The pathological hallmark underlying PD comprises the loss of the dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNpc) region and the aggregation of intracytoplasmic proteins known as Lewy bodies [8]. Treatment for PD has been progressed at different stages such developments at surgery, chemical drugs, therapies, *etc*.. have been observed. Currently, no cure is available for PD, however, these therapies and medications address some of the symptoms and improve the quality of life for patients. In the recent past, complementary and alternative therapies with herbal or ayurvedic compounds or products have shown their potential as a drug and improved the lives of patients with PD [9, 10]. As a result, many researchers are currently focusing on herbs of ayurvedic medicine to cure or reverse the symptoms of PD. A wide variety of ayurvedic herbs like "Brahmi", "Ashwagandha", "Shankhpushpi", *etc*., and their solutions, compounds, and extracts have shown very high potential as nootropic herbs to improve neurodegenerative conditions and serve as the potential therapy for neurological disorders.

THE LINK BETWEEN NEURODEGENERATION AND AYURVEDIC HERB

Ayurveda has a great emphasis on treatment and encourages the maintenance of health by paying proximate attention to a balanced lifestyle. Medical science deals with the ideas of screening, understanding, and medicinal attributes of naturally occurring plants or plant products and their role in the treatment of various diseases [11]. According to the Ayurveda, the living body is controlled by the three energies “Vata”, “Pitta”, and “Kapha” if any of these get impaired, which leads to the development of several kinds of diseases [12, 13]. The imbalance in the “Vata” leads to neurological disorders symptomized as memory loss, impaired locomotory control, anxiety, poor blood circulation, *etc*. [14]. Ayurvedic plants play a considerable role in the treatment of neurodegenerative diseases. Neurodegenerative diseases are the result of the gradual loss of the neurons in the brain, which affects many body activities such as balance, movement, talking, cognition, breathing, *etc*. [15]. These can be caused due to genetic as well as environmental factors and sometimes influenced by medical conditions like a tumor, stroke, alcoholism, *etc*.. Neurodegeneration can range from mild to chronic to life-threatening, which depends on the type of disease. There is various type of neurodegenerative disorders/disease, and some of which are:

- Alzheimer's disease
- Parkinson's disease
- Huntington's disease
- Spinal muscular atrophy
- Amyotrophic lateral sclerosis
- Friedreich's ataxia

Treatment for these diseases/disorders has been observed in the developing stage, like surgery, chemical drugs, therapies, *etc*. [16]. Currently, no cure is available for PD, however, these therapies and medications address some of the symptoms and improve the quality of life for patients. In the recent past, complementary and alternative therapies with herbal or ayurvedic compounds or products have shown their potential as a drug in animal models and improved the lives of patients with PD [9, 10]. As a result, many researchers are currently focusing on herbs of ayurvedic medicine to cure or reverse the symptoms of PD. It has been remarkably noticed in the past few years by modern sciences and epidemiological as well as experimental approaches indicating the benefits of naturally occurring plants and plant products, of Ayurveda. A wide variety of ayurvedic medicinal herbs and their extract have been used against neurodegeneration like *B. monneiri* (Bramhi), *Withania somnifera* (Ashwagandha), *Convolvulus pluricaulis*

CHAPTER 9

Diabetic Neuropathy and Neuroprotection by Natural Products

Nilay Solanki[1,*] and **Hardik Koria**[1]

[1] *Department of Pharmacology, Ramanbhai Patel College of Pharmacy, Charotar University of Science and Technology, Charusat Campus, Changa-388421(Gujarat), India*

Abstract: Diabetic neuropathy (DN) is a serious complication in type-1 diabetes and type-2 diabetes. Animal models show many abnormalities like neuropathy, hyperalgesia, allodynia, slow nerve conduction velocity (NCV), and progressive sensory and motor deficit that are associated with diabetic neuropathy. Various risk factors may be involved in causing DN, such as persistent hyperglycemia, microvascular insufficiency, oxidative stress, nitrosative stress, defective neurotrophism and autoimmune-mediated nerve destruction. Many conventional and newer therapeutic approaches are available. Approaches include effective control of glycemia. Symptoms targeted therapies such as antidepressants, SSRIs, anticonvulsants, opiates, NSAIDs and NMDA receptor antagonists. Therapies targeting particular causes include aldose reductase inhibitors, drugs that act on hexosamine pathways, protein kinase C pathways and AGE receptors. Preclinical studies involving pharmacological agents have shown positive results but were withdrawn at the stage of a clinical study, either due to lack of efficacy or due to their side effects on major organs. Medicinal herbal plants are the richest bio-resource of drugs that have been studied extensively for their neuroprotective effects. Various approaches involving neuroprotection by natural products are discussed here.

Keywords: Diabetic neuropathy, Medicinal plants, Neuroprotection, Treatments.

INTRODUCTION

The incidence of diabetes mellitus is increasing at an alarming rate and rapidly assuming epidemic proportions. India is no exception, and currently, 25 million Indians are estimated to be suffering from diabetes [1]. Further projections indicate that India will have the maximum number of diabetic patients by the year 2025 [2]. Macrovascular complications of diabetes include ischemic heart diseases, peripheral vascular disease, atherosclerosis, myocardial infarction,

* **Corresponding author Nilay Solanki:** Department of Pharmacology, Ramanbhai Patel College of Pharmacy, Charotar University of Science and Technology, Charusat Campus, Changa-388421 (Gujarat), India;
E-mail: nivyrx@gmail.com

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stroke, and gangrene, whereas microvascular complications include small vessel diseases such as retinopathy, neuropathy, and nephropathy. Neuropathy is a serious complication of type 1 (T1DM) and type two Diabetes (T2DM). Diabetic neuropathy (DN) usually occurs lately in type-1 diabetes, but it could occur early in type-2 diabetes. The prevalence of neuropathy is estimated to be about 8% in newly diagnosed patients and greater than 50% in patients with the long-standing disease [3]. There is increasing evidence that even pre-diabetic conditions are also associated with some forms of neuropathy. Diabetic neuropathy is the leading cause of non-traumatic limb amputation, and it occurs in 50% of diabetic patients. These patients suffer from severe pain. DN patients generally complain about persistent burning or tingling sensation, usually, in the legs and feet, inability to detect heat and cold, loss of vibration sensation, and the loss of pain perception; an estimated 15% of all patients with diabetes are at high risk of development of foot ulcers [4]. The selected animal model of DN should exhibit features present in human pathology. Diabetic animals show many abnormalities that are seen in diabetic patients with neuropathy, hyperalgesia, allodynia, slow nerve conduction velocity (NCV), and progressive sensory and motor deficit. Many causative factors for DN include persistent hyperglycemia, microvascular insufficiency, oxidative stress, nitrosative stress, defective neurotrophism, & autoimmune-mediated nerve destruction [3, 5 - 9]. The annual costs of diabetic neuropathy and related morbidities in the US have been estimated to exceed $10.9 billion [4]. Many approaches for the management of DN have been tested preclinically and clinically. Approaches include effective control of glycemia; Symptoms targeted therapies such as antidepressants, SSRIs, anticonvulsants, opiates, NSAIDs, NMDA receptor antagonists; Therapies targeting particular causes include aldose reductase inhibitors, drugs that act on hexosamine pathways, protein kinase C pathways, AGE receptors. Preclinical studies involving pharmacological agents have shown positive results but were withdrawn at the stage of a clinical study, either due to lack of efficacy or due to their side effects on major organs [10]. Therefore, the development of newer natural approaches for the management of diabetes and associated neuropathic changes is the need of today's world. With advancements in research, our understanding of the biochemical and molecular mechanisms leading to diabetic neuropathy has increased. At the molecular level, Adenosine and adenosine receptor agonists have been shown to have antinociceptive effects in animal models of acute and nerve injury-induced neuropathic pain [11 - 14]. Peroxynitrite mediated nitrosative stress, an initiator of DNA damage and overactivation of poly (ADP-ribose) polymerase (PARP), a nuclear enzyme activated after sensing DNA damage, are two crucial pathogenetic mechanisms in diabetic neuropathy [15]. Hyperglycaemia can induce oxidative stress through various mechanisms, such as glucose autooxidation and the resultant formation of glycation end products, dysregulation

of the polyol pathway, modifying eicosanoid metabolism, and reducing eicosanoid metabolism antioxidant defenses in diabetes [16 - 19].

DIABETES MELLITUS AND NEUROLOGICAL COMPLICATIONS

Diabetes mellitus, often simply referred to as diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin or because cells do not respond to the insulin produced. This high blood sugar produces the classic symptoms of polyuria (frequent urination), polydipsia (increased thirst), and polyphagia (increased hunger) [20, 21].

Causes of Diabetes

Following is a comprehensive list of causes of diabetes:

I. Genetic defects of β-cell Function
   a. Maturity onset diabetes of the young (MODY)
   b. Mitochondrial DNA mutations
II. Genetic defects in insulin processing or insulin action
   a. Defects in proinsulin conversion
   b. Insulin gene mutations
   c. Insulin receptor mutations
III. Exocrine Pancreatic Defects
   a. Chronic pancreatitis
   b. Pancreatectomy
   c. Pancreatic neoplasia
   d. Cystic fibrosis
IV. Endocrinopathies
   a. Growth hormone excess (acromegaly)
   b. Cushing syndrome
   c. Hyperthyroidism
   d. Pheochromocytoma
   e. Glucagonoma
V. Infections
   a. Cytomegalovirus infection
   b. Coxsackievirus B
VI. Drugs
   a. Glucocorticoids
   b. Thyroid hormone

CHAPTER 10

Autism Spectrum Disorder: An Update on the Pathophysiology and Management Strategies

Rubal Singla[1], Abhishek Mishra[1], Rupa Joshi[1], Phulen Sarma[1] and **Bikash Medhi[1,*]**

[1] *Department of Pharmacology, Post Graduate Institute of Medical Education & Research, Chandigarh-160012 (Punjab), India*

Abstract: Autism is a complex neurobehavioral and neurodevelopment disorder with impairments in sociability, language, repetitive, and restrictive stereotypical behaviour as the core symptoms. The term "autism" was first introduced in DSM-III in the year 1980; however, it was changed to autism spectrum disorder (ASD) in DSM-V. It starts in early childhood at the age of around 3 years and persists throughout life. According to data from the Centres for Disease Control and Prevention (CDC), USA, the prevalence of ASD has increased from 1 in 88 (2008 data) to 1 in 59 (2018 data). Being a complex neurological disorder, its etiology is not clear. However, numerous neurochemical pathways have been explicated that may be responsible for the development of this disorder. Besides, it has been evidenced that immune dysfunction and genetic predisposition have a major role in its progression. Some of the major neurochemical systems implicated to be involved in its etiology are glutaminergic and GABAergic as major and others such as DAergic system, adrenergic system, serotonergic system, and the endocannabinoid system. These above-mentioned pathways are crucial in the maturation and development of neurons in different parts of the brain, thus, alteration in any of these pathways enumerates a significant role in the progression of ASD. Current treatment options are antipsychotic medications, which only provide symptomatic relief for behavioral and psychiatric complications such as irritability, anxiety, mood fluctuations,*etc*.. These medications are not effective in treating the core symptoms of ASD. Given the lack of effective treatment options for ASD, drugs targeting the core pathology of the disorder are the need of the hour. Although numerous studies have discussed pharmacotherapy for ASD, the present chapter, more importantly, focuses on the available treatment options for ASD and updates on the recent research approaches for the prevention and treatment of ASD.

Keywords: Autism spectrum disorder, Antipsychotics, GABA, Glutamate, Neurodevelopment, Sociability, Stereotypy.

[*] **Corresponding author Bikash Medhi:** Department of Pharmacology, Post Graduate Institute of Medical Education & Research, Chandigarh-160012 (Panjab), India; E-mail: drbikashus@yahoo.com

Surya Pratap Singh, Hagera Dilnashin, Hareram Birla & Chetan Keswani (Eds.)

INTRODUCTION

Autism spectrum disorder (ASD) is a neurobehavioral and neurodevelopmental disorder marked by impairment in social communication and interaction along with stereotypic/repetitive behaviors [1]. The disease may also be accompanied by a diversity of comorbid conditions like anxiety, memory and learning deficits, seizures, aggressive behaviors, gastrointestinal problems, abnormalities in sensory processing, deficits in motor functioning and sleep disturbances, *etc*. [2]. ASD belongs to the umbrella heading of pervasive developmental disorders, and according to the National Institutes of Health(NIH), "The diagnostic category of pervasive developmental disorders (PDD) refers to a group of disorders that are characterized by delays of the social and communication skills [3]. The ASD includes the following five types:

• **Autistic Disorder:** This is also known as the classic autistic disorder. The children with this disorder show the standard behavioral signs of autism, such as deficits in social behavior, stereotypical patterns, social isolation, problems with communication and understanding, hypersensitivity, and little to no eye contact. They are sensitive to physical touch, high noises, and bright colors.

• **Asperger's Syndrome:** The children with this disorder are often misdiagnosed as obsessive-compulsive disorder or attention deficit disorder, find difficulties in understanding and interpreting social cues, and show an obsessive interest in specific subjects. These children often have high intelligence levels and may often be referred to as "high functioning autism" [4]. They may also suffer from sensory challenges, such as sensitivity from a shirt's tag. This disorder is three times more common in boys than girls.

• **Rett's Disorder**: This disorder only affects girls and starts when the child reaches about 6 months of age [5]. The children with this disorder show similar symptoms to other forms of autism, such as repetitive behaviors and speech and motor activity delay. Moreover, other symptoms such as grinding of the teeth, delays in growth, breathing problems, and mental retardations may aggravate as the age increases.

• **Childhood Disintegrative Disorder:** This form is considered the rarest type of autism. The children with this form of autism seem normal in the initial years but start to suddenly regress after 2 -3 years of age and stop interacting or talking. They suddenly lose multiple areas of function such as social skills, speech, and mental abilities, and the impairment is severe with a very less chance of recovery of the lost functions. This disorder is also linked to the development of seizures.

• **Pervasive Developmental Disorder not Otherwise Specified:** This term is often used for those autistic children that do not properly fit into one criterion of a specific diagnosis. This disorder is characterized as a mild form of autism in which children may show developmental and social-behavioral delays such as delays in walking/ talking than normal children. However, the children with this disorder find it easy to cope with challenges as compared to children with the more severe autism types [6].

HISTORY

Autism was separated from schizophrenia in 1938. A detailed description of autistic disorders was described by Leo Kanner in 1943 [7]. He described the similarities in the behaviors such as autistic aloneness and insistence on the sameness of 11 children to define infantile autism. The broader categories of autism were explained by Rutter [8]. The research by Hans in the Vienna University Hospital led to be known as Asperger syndrome. The milder form of Kanner's autism was then called Asperger syndrome. Then, the other terms like autistic spectrum disorder and Pervasive developmental disorder not otherwise specified came into use.

EPIDEMIOLOGY

The data by the Centre for Disease Control and Prevention (CDC) suggests that1 54 children suffer from ASD [9]. ASD prevalence in 2020 was 18.5 per 1,000 (1 in 54), and it is 4.3 times more common in boys than girls (1 in 37 boys and 1 in 151 girls). According to the CDC2020 report, ASD is the fastest-growing developmental disability. Literature shows 1% in the United Kingdom and 1.5% in the United States, and 2 million children are diagnosed with ASD in India [10].

AUTISM SYMPTOMATOLOGY

Impaired Social Behavior

Impaired social behavior is one of the core diagnostics features as well as an interfering symptom of autism. It includes social exile, difficulty in communication, avoidance of eye contact, and impaired language skills.

CHAPTER 11

Neuroprotective Effect of *Ginkgo Biloba* and its Role in Alzheimer's Disease

Divya Raj Prasad[1,*], **Bipin Maurya**[2,*] and **Aparna Mishra**[3]

[1] *Department of Genetics and Plant Breeding, Institute of Agricultural Sciences, Banaras Hindu University, Varanasi-221005 (U.P.), India*

[2] *Laboratory of Morphogenesis, Centre of Advance Study in Botany, Institute of Science, Banaras Hindu University, Varanasi-221005 (U.P.), India*

[3] *Department of Bioscience and Biotechnology, Banasthali Vidyapith University, Banasthali-304022 (Rajasthan), India*

Abstract: Alzheimer's disease (AD) is a common age-related neurodegenerative disorder that results in cognitive defects. The disease is a progressive, age-associated, irreversible, neurodegenerative disease with severe memory loss, personality changes, unusual behavior and impairment in cognitive function. There is no cure for AD, and the drugs available for the treatment of the disease have limited efficacy. Medicine develops from the extract of medicinal plants have been the single most productive and common source for the development of drugs, and also, more than thousands of new products are already in clinical study. Different types of therapeutic strategies like herbal and synthetic approaches are being used against AD on the basis of understanding AD mechanisms. *Ginkgo biloba* extract (GBE) is the most effective and highly investigated, herbal medicine for AD and other cognitive disorders. One of the famous dietary supplements is GBE, consumed by the elderly population to improve memory and age-related loss of cognitive function. The exact mechanism of action of *Ginkgo* extract in AD is still not very clear. The phytochemical studies of the different plant parts of the *G. biloba* have revealed the presence of many valuable secondary metabolites, such as flavonoids, polyphenols, triterpenes, sterols, and alkaloids that shows a wide spectrum of pharmacological activities like anti-amyloidogenic, anti-inflammatory and antioxidant effects. This book chapter gathers research on the *G. biloba* plant and its neuroprotective and phytochemical effects, which are used against AD. The summarized information concern pharmacological activities, neuroprotective effect, and biological and clinical applications of the *Ginkgo* plant.

Keywords: Alzheimer's disease, *Ginkgo biloba*, Neuroprotective, Phytochemical.

[*] **Corresponding authors Bipin Maurya & Divya Raj Prasad:** Laboratory of Morphogenesis, Centre of Advance Study in Botany, Institute of Science, Banaras Hindu University, Varanasi-221005 (U.P.), India and Department of Genetics and Plant breeding, Institute of Agricultural Sciences, Banaras Hindu University, Varanasi-221005 (U.P.), India; E-mails: bipinmaurya841@gmail.com and divyarajbhu@gmail.com

Surya Pratap Singh, Hagera Dilnashin, Hareram Birla & Chetan Keswani (Eds.)

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurological disorder of the brain that was first described in the year of 1906 and named after German physician Aloes Alzheimer. It is the most common form of dementia which affects an estimated count of 10 million people across the world [1]. The major symptoms of this disease are impairment of memory and, eventually, the disturbance in language, planning, perception and reasoning, and symptoms appear gradually. AD is an irreversible, age-associated, progressive neurodegenerative, characterized by severe memory loss, personality changes, unusual behavior and a decline in cognitive function [2, 3]. This disease is often seen in people aged 65 and older than that and one-third of those aged 85 or above to this age. The term dementia is generally used for the loss of memory and other cognitive disabilities that seriously interfere with daily routine. There are many different types of dementia, such as Parkinson's disease with dementia, vascular dementia, frontal temporal dementia (FTD), reversible dementia, Korsakoff's syndrome, Posterior cortical atrophy (PCA), Down syndrome dementia and dementia with Lewy bodies. According to a scientific report, an estimated 5.4 million American population was living with AD. In the United States, an estimated population of 930,000 people could be living with Parkinson's disease by the year 2020. The collection of electronic Databases like Pub Med, Cochrane Library, MEDLINE, and Center Watch Trials Database journal articles was used in the research for information and spreading awareness related to the above disease. The database search consoled the terms dementia, AD, phytochemical analysis, etc. The brain is made up of 100 billion nerve cells, and each cell connects to other cells to form huge communication networks. Each group of nerve cells has its unique jobs [4 - 6].

Some cells are active in learning, thinking, and memory; another group helps us smell, sight, hear, and coordinate our muscles when to move. Our brain cells operate like tiny factories that further receive the supplies, construct equipment, generate energy, and eliminate waste. Many functions are controlled by the brain and body, which needs a large amount of fuel and oxygen and coordination between organs. Extracellular deposits of aggregated amyloid-protein (Aβ) in the brain parenchyma and Cerebral blood vessels, cerebral amyloid angiopathy (CAA) is one of the pathological hallmarks of AD [7]. Due to the deposition of high levels of fibrillar Aβ in AD, the brain is associated with loss of synapses, impairment of neuronal functions, and loss of neurons. Aβ was sequenced from meningeal vessels and senile plaques of AD patients and individuals with Down's syndrome [8]. Scientists still have not discovered a complete treatment and cure for AD. Neuropathological genetic and biochemical data suggest that Aβ aggregation is the main reason for the initiation of AD pathogenesis,

neurofibrillary pathogen strongly related to neuronal dysfunction and development of the clinical phase of AD. The clinical phase of AD is also recognized by neurotransmitter loss, synaptic loss, and neuroinflammation selective neuronal death [9]. That's why AD creates a serious problem in the whole world. It believes that therapeutic intervention that could postpone the onset or progression of AD would reduce the number of cases in the upcoming next 50 years. In the current scenario, scientists need more accurate scientific knowledge for awareness, prevention and treatment of diseases like AD and dementia [3, 10 - 12].

Herbal medicine offers several options to control the method of symptoms diagnosis, prevention and progression of AD. There has been a new trend coming for the preparation and marketing of herbal drugs based on medicinal herbs, so the scientific and commercial significance of those drugs appear to be gaining momentum in the health system. These plant-derived herbal drugs were carefully standardized, and their efficacy and safety for a specific health problems have been identified [13, 14].

The past decade has also increased awareness and intensified the interest in herbal drugs in which phytochemicals constitute can have long-term benefits for human health. Medicinal herbs are well known for their potent source of many antioxidants and phenolic compounds. Among these organic compounds in herbal plants, polyphenols have been recognized for their antioxidant activity and many more health benefits. Natural antioxidants and free radical scavengers like phenolic compounds and flavonoids have become of substantial interest among scientists due to their health benefits in the food and pharmacological industry [15 - 18].

Many Phytochemicals found in vegetables and fruits are believed to reduce the risk of several diseases like cancers, cardiovascular diseases and neurodegenerative disorders. Therefore, those populations who consume a high amount of vegetables and fruits have a reduced risk for such diseases that are caused due to neuronal dysfunction [19]. Herbal medicines have been used for a long time to treat neural disorders [5, 20, 21].

Ginkgo biloba (Ginkgoaceae) is the best and most well-known herb for AD and its associated symptoms. *G. biloba* tree, also called "a living fossil," has a life span of approx. 4000 years, possibly because of its resistance to infections and high tolerance to pollution [22]. *G. biloba* is generally called a living fossil, maidenhair tree, ginkyo, kew tree, yinhsing and is considered native to China, Japan and Korea. Now, it is widely cultivated for its leaves and nuts for commercial use [6, 12].

CHAPTER 12

Role of *Withania somnifera* (Ashwagandha) in Neuronal Health

Ambarish Kumar Sinha[1], Hagera Dilnashin[2], Hareram Birla[2] and **Gaurav Kumar[1,*]**

[1] *Department of Clinical Research, School of Biosciences and Biomedical Engineering, Galgotias University, Greater Noida, Uttar Pradesh, India*

[2] *Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi 221005(U.P.), India*

Abstract: Neurodegenerative disease refers to the progressive deterioration of neurologic function which leads to loss of speech, vision, hearing, and movement. It is also associated with seizures, eating difficulties, and memory impairment. Natural products have emerged as potential neuroprotective agents for the treatment of neurodegenerative diseases due to the enormous adverse effects associated with pharmacological drugs. *Withania somnifera* (Ashwagandha) is a traditional Ayurvedic medicine, used in India as a general tonic. It contains withanolides, and phytochemicals that may have adaptogenic properties. Studies show that *W. somnifera* is a neuroprotective agent and can protect the brain from oxidative stress and inflammation. This explains its ability to protect from mood disorders. In this review, we have reviewed the available evidence of *W. somnifera* and its phytochemicals for neurodegenerative disorders.

Keywords: Ayurvedic medicine, Chinese medicine, Neurological diseases, Phytochemicals, *Withania somnifera*.

INTRODUCTION

Neurodegenerative diseases are a heterogeneous group of disorders that are characterized by the progressive degeneration of the structure and function of the central nervous system (CNS) or peripheral nervous system (PNS). Neurodegenerative diseases are incurable and debilitating conditions that result in progressive degeneration and/or death of nerve cells. Neurodegenerative diseases represent a major threat to human health. Most common neurodegenerative

* ***Corresponding author Gaurav Kumar:** Department of Clinical Research, School of Biosciences and Biomedical Engineering, Galgotias University, Greater Noida (U.P.), India; E-mail: gaurav.rs.bme14@iitbhu.ac.in

Surya Pratap Singh, Hagera Dilnashin, Hareram Birla & Chetan Keswani (Eds.)

diseases include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia, and, the spinocerebellar ataxias. *Withania somnifera* (Ashwagandha) is one of the most potent and most versatile drugs used in traditional systems of medicine. *W. somnifera* has been traditionally used for the treatment of general debility, nervous exhaustion, insomnia, memory loss, etc. Ashwagandha has been reported to be used in over 300 formulations in the traditional systems of medicine such as Ayurveda, Siddha, and Unani [1 - 5]. These traditional uses suggest that Ashwagandha might help treat neurodegenerative diseases and brain health in general (Fig. **1**). Several studies have reported the anti-inflammatory, anti-tumor, antioxidant, immunomodulatory, and anti-neuropsychiatric activity of Ashwagandha (Fig. **2**). In this chapter, we discuss the evidence of various health benefits of Ashwagandha in neurological diseases.

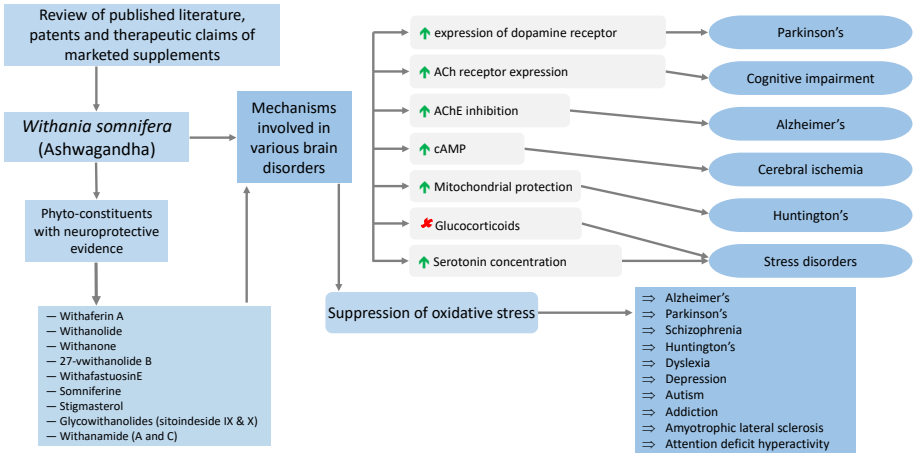

Fig. (1). Summary of neuroprotective constituents of Ashwagandha and related mechanism in brain disorder.

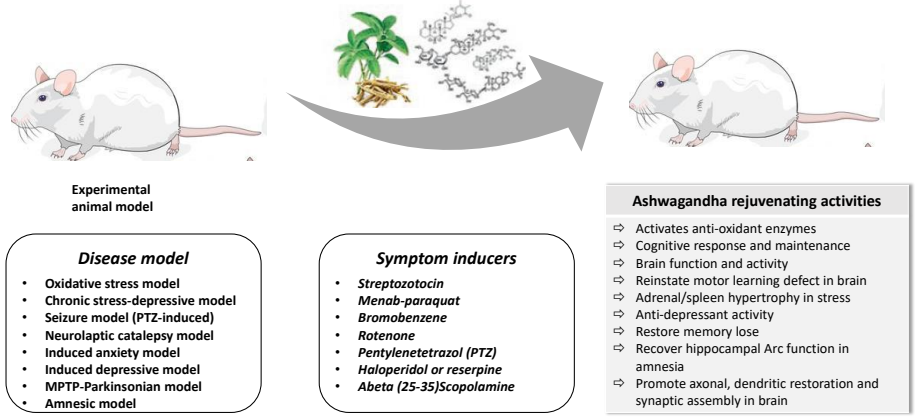

Fig. (2). Molecular activities of Ashwagandha have been validated in various animal models.

CHEMICAL COMPOSITION OF ASHWAGANDHA

Natural products have been used since ancient times for their therapeutic properties and have emerged as a preferred choice of treatment due to the large number of safety concerns associated with pharmacological drugs. Ashwagandha (*Withania somnifera*) also known as "Indian winter cherry" is a perennial plant that belongs to the *Solanaceae* family. The roots of Ashwagandha smell like a horse ("ashwa" in Sanskrit), therefore it is named Ashwagandha. Herbalists also call Ashwagandha "Indian ginseng" because in the Ayurvedic system of medicine, it is used similarly as the Panax ginseng is used in the Traditional Chinese Medicine (TCM). Table **1** lists the mechanism of Ashwagandha and its phytochemicals used in neurological disease models. The major constituents of the Ashwagandha are steroidal alkaloids and steroidal lactones which are collectively called withanolides. Withanolides are naturally occurring C-28 steroidal lactones built on an intact ergostane structure, in which C-22 and C-26 are oxidized to form a six-membered lactone ring. The basic structure of withanolides is made up of 22-hydroxy-ergostan-26-oic acid-26, 22-lactone, and is called the "withanolide skeleton" [5 - 10]. To date, twelve alkaloids, thirty-five withanolides, and a few sitoindos have been identified and investigated in neurological disease. Apart from withanolides, other alkaloid constituents of Ashwagandha include: somniferine, somnine, somniferinine, withananine, pseudo-withanine, tropine, pseudotropine, 3-a-gloyloxytropane, choline, cuscohygrine, isopelletierine, and anaferine andanahydrine. To date, various products/formulations of Ashwagandha are developed and commercially available. Table **2** outlines some commercially available formulations of Ashwagandha and their associated health claims.

Table 1. Some commercially available formulations of Ashwagandha and associated health claims

S. No.	Product	Manufacturer	Health Claim
1	Neuro Response™	INNATE Response	Support for stress
2	Adrenal Response®	INNATE Response	Support for stress
3	Mito2Max	doTERRA International	Supports healthy cellular energy production and optimal mitochondrial function
4	Integrative Therapeutics® HPA Adapt™	Integrative Therapeutics	Support for stress
5	Ashwagandha	Pure Encapsulations®	Support for occasional stress
6	Daily Stress Formula	Pure Encapsulations®	Promotes mental relaxation and moderates the effects of occasional stress

CHAPTER 13

Modulation of Proinflammatory Cytokines by Flavonoids in the Main Age-related Neurodegenerative Diseases

Héctor Eduardo López-Valdés[1,*] and **Hilda Martínez-Coria**[1]

[1] *Departamento de Fisiología, Facultad de Medicina,Universidad Nacional Autónoma de México (UNAM), Ciudad de México, México*

Abstract: Aging is a process associated with distinctive changes in physiological functions and physical appearance that result from progressive tissue degeneration, harming the structure and function of vital organs. Illnesses that are particularly frequent in people 65 years of age and older are generally grouped as age-related diseases or aging-related diseases and include neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD), which are caused by progressive degeneration and/or neuronal death to produce debilitating conditions, and they have no cure. For these illnesses, the most important risk factor is aging. Aging involves changes in neuroendocrine and inflammatory responses and presents a stage with chronic and low-grade inflammation, characterized by a general increase in the production of proinflammatory cytokines, inflammatory markers, and cellular senescence. Herbal medicine, as well as various components of the human diet, including vegetables, cereals, and fruits, contain widely varied phytochemicals including flavonoids, which are the most common polyphenolic compounds. Epidemiological studies suggest that a higher intake of flavonoid-rich foods and beverages is associated with better cognitive outcomes, lower dementia rates, and reduced risk of neurodegenerative diseases. Moreover, numerous preclinical studies have shown that these compounds have a therapeutic effect on animal models of human degenerative diseases and highlight the anti-inflammatory effect of flavonoids by decreasing the activated glial cells and several proinflammatory mediators. Much modern scientific research has focused on establishing biological activities of purified single compounds to provide an evidence base for the rationale of traditional practice, and also to integrate these into modern medical practice.

Keywords: Aging, Age-related diseases, Flavonoids, Neurodegenerative diseases.

[*] **Corresponding author Hector Eduardo Lopez Valdes:** Departamento de Fisiología, Facultad de Medicina, Universidad Nacional Autónoma de México (UNAM), Ciudad de México, México; E-mail: helopezv@gmail.com

Surya Pratap Singh, Hagera Dilnashin, Hareram Birla & Chetan Keswani (Eds.)

INTRODUCTION

Aging is an irreversible and inevitable process associated with distinctive changes in physiological functions and physical appearance, that result from progressive tissue degeneration, harming the structure and function of vital organs [1]. For the vast majority of chronic diseases, including chronic obstructive pulmonary disease (COPD), atherosclerosis, hypertension, osteoporosis, osteoarthritis cardiac failure, type 2 diabetes, metabolic syndrome, chronic renal disease, neurodegenerative diseases, and cancer, the most important risk factor is aging [2, 3]. Neurodegenerative diseases are a heterogeneous group of conditions caused by progressive degeneration and/or neuronal death to produce debilitating conditions and have no cure. These groups include Alzheimer's disease (AD), vascular dementia (VaD), Lewy body dementia (LBD), Parkinson's disease (PD) Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and frontotemporal dementia [4, 5]. Herbal medicine, as well as components of the human diet, including teas, wine, vegetables, cereals and fruits, contains varied phytochemicals including flavonoids, which are the most common polyphenolic compounds [6]. Numerous preclinical studies have shown that these compounds have a therapeutic effect on animal models of human degenerative diseases. The mechanism and active compounds for most of the herbs used in medicine are still not well-defined because they contain multiple bioactive molecules and consequently can modulate multiple pharmacologic targets. This rich source of bioactive molecules has been the subject of much modern scientific research, concentrating mainly on establishing biological activities of purified single compounds to provide an evidence base for the rationale of traditional practice, and also to integrate them into modern medical practice [7].

In the sections below, we will describe the basic knowledge of flavonoids, aging, neuroinflammation, AD, PD, and HD, and we will provide an overview of the evidence relating to the anti-inflammatory effects of single flavonoids in different model systems of these diseases.

FLAVONOIDS

Flavonoids are the most common group of plant polyphenols, they are present in all vascular plants and have a wide range of functions in plant biochemistry, physiology, and ecologies, such as coloration of flower petals, fertility, and pollen germination, and in protection against ultraviolet light. Moreover, a single plant will often contain several dozens of different flavonoids [8]. Flavonoids are low-molecular-weight phenolic compounds that are widely distributed in the plant kingdom and are the main phytochemicals found in more than 6000 species of

plants, and they also are abundantly found in foods and beverages of plant origin, including vegetables, fruits, grains roots, wine, tea and cocoa [9].

Structurally, flavonoids occur as glycosides, methylated derivatives, and aglycones, and the latter of which represent the basic structure that has a shared C6–C3–C6 structure containing two aromatic rings (A and B rings) that are linked by a three-carbon bridge (Fig. **1**), creating an oxygenated heterocycle. This type of structure is commonly divided into subclasses based on the connection of the B ring to the C ring, as well as the oxidation state and functional groups of the C ring [10]. Depending on the carbon of the C ring on which the B ring is attached and the degree of unsaturation and oxidation, flavonoids can be subdivided into different subgroups such as flavones, flavonols, flavanones, flavanonols, flavanols (or catechins), anthocyanins, chalcones, and isoflavonoids [9] (Fig. **1**).

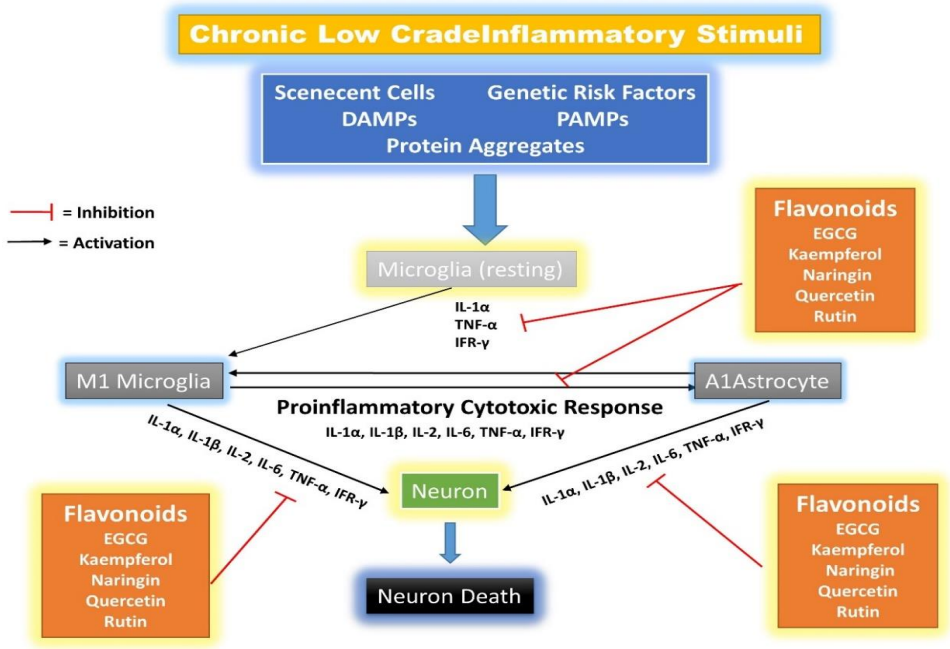

Fig. (1). Basic structure of flavonoid and flavonoids subgroups. Below of each flavonoid subgroup, some representative compounds.

To be absorbed from the small intestine upon ingestion, the flavonoids contained in foods and beverages must be in the aglycones form to allow them to pass from

CHAPTER 14

Utilization of Nutraceuticals and Ayurvedic Drugs in the Management of Parkinson's Disease

Shilpa Negi[1] and **Sarika Singh**[1,*]

[1] *Department of Neuroscience and Ageing Biology and Division of Toxicology and Experimental Medicine, CSIR-Central Drug Research Institute, Lucknow-226031, (U.P.), India*

Abstract: Age-related degeneration of dopaminergic (DAergic) neurons may be either genetic or due to exposure to environmental toxins that mark the onset of Parkinson's disease (PD) pathology. Treatments like surgery and symptoms relieving drugs are available, but they have their side effects during prolonged consumption. Recent studies have shown that the use of food-derived compounds offers significant prevention and treatment of many neurological disorders. These compounds, commonly known as nutraceuticals, show immense importance in mitigating neuronal disease as there is a strong correlation between food and mental health. Accumulation of α-synuclein protein in the degenerated neurons and concomitant oxidative stress-related pathological events are critical and known pathological markers of PD therefore, food-derived compounds containing antioxidative capacity may offer therapeutic implications. In addition, nutraceuticals are comparatively cost-effective and the safest alternatives of drugs available. Indian medicine system of Ayurveda has long been incorporating the use of herbs to cure PD. This chapter focuses on the utilization of nutraceuticals and ayurvedic preparations in PD pathology.

Keywords: Ayurvedic drugs, DA agonists, Nutraceuticals, Therapeutics, PD.

INTRODUCTION

Parkinson's Disease (PD) is a neuropathological condition associated with progressive deterioration of dopamine (DA) secreting neurons in the substantia nigra pars compacta (SNpc) region of the midbrain [1]. Extensive research has identified various genetic mutations that induce the PD, however, the majority of the PD cases are sporadic or idiopathic, therefore, environmental exposure also plays a critical role in disease onset [2]. Idiopathic PD is induced due to exposure to several chemical and environmental toxins, such as rotenone, paraquat, *etc*.

* **Corresponding authors Sarika Singh:** Department of Neuroscience and Ageing Biology and Division of Toxicology and Experimental Medicine, CSIR-Central Drug Research Institute, Lucknow-226031, (U.P.), India;
E-mail: sarika_singh@cdri.res.in

Surya Pratap Singh, Hagera Dilnashin, Hareram Birla & Chetan Keswani (Eds.)

Rotenone, 1-Methyl-4-Phenyl-1, 2, 3, 6-Tetrahydroxypyridiine (MPTP), 6-Hydroxydopamine (6-OHDA) etc., are successfully being utilized in research to induce PD-related pathology in both cellular and rodent models to elucidate the disease mechanisms [3]. These toxins interact with and modulate the functions of various genes like SNCA/alpha-synuclein (α-syn), Ubiquitin carboxy-terminal Hydrolase-1 (UCHL1), Leucine Rich Repeat Kinase-2 (LRRK-2), Serine Protease (HTRA2), Parkin (PRKN), PTEN-Induced Putative Kinase 1(PINK), Lysosomal ATPase and Glucocerebrosidase (GBA) whose mutation or alteration in protein structure & function is responsible for the induction of disease pathology [4]. Symptomatically PD pathology involves tremor, rigidity, bradykinesia (slowness of movement), and postural instability [5]. Including these motor disabilities, various non-motor clinical features are also associated with the disease and advancing age. These non-motor symptoms include neuropsychiatric symptoms (depression, dementia, panic attacks, hallucinations etc.), sleep disorders (insomnia, restless legs, periodic limb movement, etc.), nausea, constipation, dry eyes, etc [6 - 10]. Biochemical pathogenesis of PD involves the misfolding and aggregation of protein alpha-synuclein (which accumulate along with chaperones and ubiquitin residues in the Lewy bodies found in DAergic neurons undergoing degeneration), unfolded protein response (UPR) and endoplasmic reticulum-associated degradation (ERAD), oxidative & nitrosative stress, mitochondrial dysfunction and altered bioenergetics which disturbs the neuronal physiological functions and promote the mitophagy and apoptosis. Although, SNpc has neuromelanin that offers neuroprotective effects, the high level of iron in SNpc activates the monoamine oxidase B (MAO-B), which participates in DA metabolism and forms the neurotoxic H_2O_2 [3, 11]. Downstream cellular signalling or mechanisms of PD are not intensively known, nonetheless, pathways involving oxidative stress and protein misfolding work in a feedback route and induce the apoptosis of neurons. Current treatment of PD includes drugs like Levodopa (L-Dopa), DA agonists (pramipexole, lisuride, cabergoline), and MAO-B inhibitors (selegiline and rasagiline), while deep brain surgery and implantation of embryonic DAergic neurons (gene therapy) are also employed but limited to very few patients due to its high cost [4]. Despite the available complicated surgeries and various medications, no therapeutic strategy could modify the disease status and prevent neuronal degeneration. Therefore, further review of available research and the therapeutic molecule is needed. Since synthetic drugs are not offering the disease modifications now, researchers are looking for nutraceuticals that may have comparatively fewer side effects and better therapeutic implications. Nutraceuticals are the top priority in this category as they are readily available, comparatively have fewer side effects, and are cost-effective. The term Nutraceutical was coined by Dr. De Felice, which refers to food or bioactive compounds derived from food that has therapeutic benefits in

the prevention and/or in the treatment of chronic diseases like PD [1, 2, 12 - 14]. These nutraceuticals are crucial as they have Antioxidative capacity. Since PD pathology involves oxidative neuronal apoptosis, these nutraceuticals offer therapeutic implications but still, the pre-clinical studies are limited and further explorations are required.

NUTRACEUTICALS USED IN PD THERAPEUTICS

Various nutraceuticals have been tested for their effects on cell culture and animal models in the perspective of PD pathology, mainly targeting the mechanisms including (a) reactive oxygen species (ROS) scavenging (b) anti-inflammation (c) iron-chelation (d) modulation of cell signaling pathway (e) mitochondrial function restoration and (f) anti-apoptosis (Fig. **1**) [3]. L-Dopa is the potential synthetic drug given to PD patients along with carbidopa, however, it shows significant side effects after chronic consumption [4, 15 - 19]. Nutraceuticals on the basis of their natural resource, may be of different types, and three key terms are being used for them 1. Nutrients 2. Herbals 3. Dietary supplements/fibers. Globally, the most rapidly growing segment of the industry is dietary supplements, and they also offer significant health improvements [20 - 25]. In a study by Zhao *et al.* (2007), the twenty-four genera of plants have been reviewed and suggested to have therapeutic implications in PD and readers may refer to the article [26, 27]. Phytochemicals like ginsenosides, curcumin, asiatic acid, etc., have well-known therapeutic potentials. Also, nutrients like co-enzyme Q_{10}, Nicotinamide adenine dinucleotide (NADH), vitamin C, etc., can be obtained from fruits or other parts of plants and act as anti-oxidants. Extracts of *Panax ginseng* contain ginsenosides $Rb_{1,}$ $Rg_{1,}$ Re, and Rd, known for their neuroprotection, anti-inflammatory, anti-oxidant and anti-apoptotic properties [26]. *Gastrodia*, an herbal medicine used in oriental countries, has anti-oxidative properties due its constituents like vanillyl alcohol, 4-hydroxybenzaldehyde, etc. and can cross the blood-brain barrier, which is the most important concern during drug development for neurodegenerative disorders [28]. Resveratrol obtained from grapes, peanuts, berries, and pines acts as a ROS scavenger [28]. Catechins from green tea act as anti-oxidant and restore catalase activity [29]. The details of various nutraceuticals are given in Table **1**.

Table 1. Neutraceutical explored in experimental models of PD.

Bioactive Compound	Model	Mechanism of Action	Refs.
Omega-3-Polyunsaturated Fatty acid from fish	MPTP-induced mice	Reduce DA oxidation and important modulators of DAergic neurons in basal ganglia.	[3]
Coenzyme Q_{10}	MPTP-induced rodent	Maintains Electron Transport Chain of mitochondria.	[3, 4]

CHAPTER 15

Systems Analysis Based Approach for Therapeutic Intervention in Mixed Vascular-Alzheimer Dementia (MVAD) Using Secondary Metabolites

Anindita Bhattacharjee[1] and **Prasun Kumar Roy**[1, 2,*]

[1] *Neuroimaging Laboratory, School of Bio-Medical Engineering, Indian Institute of Technology, Banaras Hindu University, Varanasi-221005 (U.P.), India*

[2] *Centre for Tissue Engineering, Indian Institute of Technology, Banaras Hindu University, Varanasi-221005 (U.P.), India*

Abstract: Mixed dementia is a form of dementia where Alzheimer's dementia coexists with vascular dementia (VaD) in the same patient. Currently, the treatment available for mixed dementia is conventional Alzheimer's dementia therapy dispensing symptomatic relief. We aim to delineate the therapeutic possibility of some secondary metabolites, which can provide manageable intervention because of their multi-targeting and multiple pathophysiological components of Alzheimer's dementia and VaD. We performed the acquisition of relevant information and data by accessing and analyzing Pubmed, Science Direct, Google Scholar, and Scopus sources, to assess the validity of therapeutic use of secondary metabolites against mixed dementia. For the initial acquisition of data (*in vitro*, *in vivo*, and clinical), the keywords that were used were "secondary metabolites," "plant extract," "mixed dementia," "Alzheimer's disease," and "vascular dementia." All types of relevant research articles, review articles, and books were included. In our study, clinically, preclinical, *in vivo*, and *in vitro* studies of secondary metabolites are encompassed. Furthermore, we undertook the formulation of the mechanism of action of secondary metabolites in terms of systems biology-oriented analysis and signal transduction-based methodology. Firstly, the likely mechanisms through which mixed dementia can take place are identified and analyzed rigorously. Secondly, we demarcate the pharmacological actions of the secondary metabolites in treating mixed dementia by (i) Targeting acetylcholine levels, (ii) Reducing or dissociating amyloid-beta (Aβ) load, (iii) Modulating microglial activation, and (iii) Providing vasodilation concurrently with their various constituents of Alzheimer's dementia and VaD. Thirdly, we formulate how several preclinical and clinical studies furnish evidence that secondary metabolites may have efficacy in Alzheimer's patients with cerebrovascular disorders.

We formulate comprehensive evidence to substantiate the use of secondary metabolites from medicinal plants to enhance therapeutic intervention in mixed dementia.

* **Corresponding authors Prasun Kumar Roy;** Centre for Tissue Engineering, Indian Institute of Technology, Banaras Hindu University, Varanasi-221005 (U.P.), India; E-mail: pkroy.bme@iitbhu.ac.in

Surya Pratap Singh, Hagera Dilnashin, Hareram Birla & Chetan Keswani (Eds.)

Keywords: Alzheimer disease, Mixed dementia, Plant extract, Secondary metabolites.

INTRODUCTION

As the name implies, mixed dementia is the clinical situation where Alzheimer's disease (AD) and cerebrovascular disease (CVD) exist in the same demented patient. The co-occurrence of neurodegenerative and vascular diseases is more in elderly patients since both conditions are age-dependent. According to the World Health Organization (WHO), the most common form of dementia is AD, whose prevalence is approximately 60-70%, and another crucial form of dementia is vascular dementia (VaD) (≈25-30%). Globally, 22% of the population exhibit coexistence of these two forms of dementia [1].

Given Alzheimer's dementia and VaD's clinical presentations overlap, the distinction between these diseases is challenging. A mixed dementia diagnosis can be made using the clinical/neuroimaging criteria of possible AD and vascular cognitive impairment (VCI) as separate entities. Alzheimer's patients with multiple vascular or ischemic brain lesions identified from autopsy studies can provide evidence for pathologic diagnosis [2]. This concomitant occurrence has neuropathological evidence delineating the connection between AD and CVD. Clinico-pathological correlation using guidelines of (i) National Institute of Neurological and Communicative Disorders and Stroke and (ii) Alzheimer's Disease and Related Disorders Association and (iii) Consortium to Establish a Registry for Alzheimer's Disease Criteria, as performed by Lim, Tsuang, *et al*., show that 60% cases of AD patients had co-existing vascular or Parkinson's disease (PD) lesions [3].

Along with the adequate diagnosis of each type of dementia, a proper treatment schedule needs to be introduced for optimal treatment. Currently, predominant pharmacotherapy is symptomatic and preventive, often leading to several adverse effects. Secondary metabolites obtained from bacteria, fungi, or plants can provide a therapeutic regimen with lesser adverse effects. Plant metabolites used to modulate blood pressure could also be explored for mixed dementia treatment.

METHODS

Firstly, we have undertaken the acquisition of pertinent information and data by analysis of Pubmed, Science Direct, Google Scholar, and Scopus platforms. We obtained the assessment of the feasibility and validity of therapeutic interventions utilizing secondary metabolites against mixed dementia. We used the keywords “secondary metabolites,” “phytochemical”, “plant extract,” “mixed dementia,” “Alzheimer's disease,” and “vascular dementia.” We analyzed different research

articles, review articles, monographs, books, and treatises. For data acquisition, we provided attention to a successively higher level of the investigations (molecule-based bioinformatics, cell-based *in vitro*, animal-based *in vivo*, and human-based clinical studies). Maximal studies were bound to the period between 1990 and 2020. We have queried the keywords in specific textual fields (title, abstract, and, if available, subject). The only inclusion criterion was that the investigation should be available as full text in any bibliographic or academic databases.

Secondly, we then performed an integrative analysis of the information and data available, from the framework of systems biology modulation, signal transduction pathway profiling, and general systems analysis approach. We particularly considered the input-output analysis model, where, using the signal operations framework, the successive processes are Signal Input, Signal Transmission, Signal Modulation, and Signal Output (Fig. **1**).

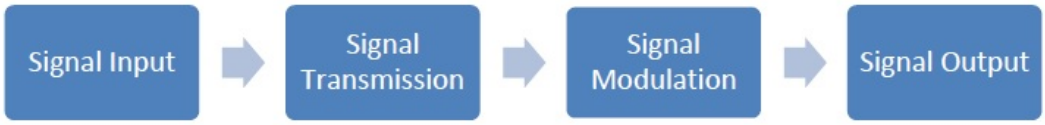

Fig. (1). The components of signal operations from the Systems Analysis framework.

Thirdly, we have thereby also proposed a likely plausible mechanism of action behind mixed vascular alzheimer's dementia, and the effects of secondary metabolites of the disease, utilizing the information accessed, analyzed, and assessed. Moreover, we have significantly validated the therapeutic interventional role of secondary metabolites in mixed dementia, including that with rigorous clinical trial data, founded on reliable *in vitro* cell line studies and *in vivo* animal studies.

PATHOGENESIS OF MIXED DEMENTIA

The pathogenesis of mixed vascular Alzheimer's dementia is unknown. However, two theories contribute to this disease state: amyloid theory and vascular theory. The amyloid theory encompasses an accumulation of amyloid-beta (Aβ) plaques in brain tissue, causing a reduction of cerebral blood flow to give rise to cognitive decline [4]. On the other hand, regarding the vascular aspect, various lifestyle diseases, such as diabetes mellitus, hypertension, cardiac ailments, and obesity can cause vascular changes, for instance, the thickening of blood vessels, causing cerebral atrophy [5]. The following vascular damages characterize the vascular theory with aging:

SUBJECT INDEX

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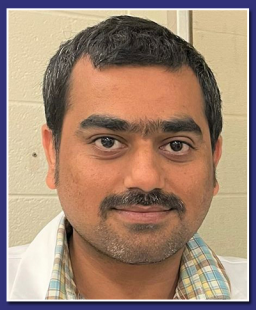
Surya Pratap Singh

Prof. Surya Pratap Singh is the Head of the Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, India. Previously, he has worked at AIIMS, New Delhi, University of Illinois, and John Hopkins Medical Institute, Baltimore, USA. He is a life member of the Endocrine Society, USA. His research team is focused on discovering novel neuroprotective herbal formulations against neurodegenerative diseases. Moreover, he has successfully isolated, formulated, and patented various secondary metabolites from medicinal plants having neuroprotective roles.

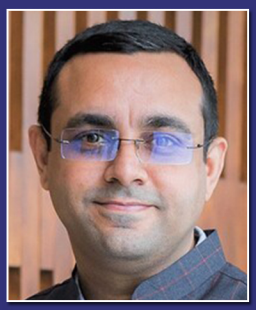
Hagera Dilnashin

Dr. Hagera Dilnashin is a Senior Research Fellow in the Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, India. Her doctoral research investigates the use of herbal medicines as an alternative for the treatment of neurodegenerative disorders like Parkinson's disease. She has published more than 10 research articles and contributed book chapters in leading journals like Neurotoxicity Research, CNS and Neurological Disorders, Journal of Neurochemistry, etc. She is a member of Indian Academy of Neuroscience and International Parkinson and Movement Disorder Society. She has done 18 peer-reviewed papers in the journals for e.g. Archives of Phytopathology and Plant Protection, Taylor & Francis, Indian Phytopathology, Springer Nature, and Oxidative Medicine and Cellular Longevity. She also has keen interest in thematic philately like crane, parrot, etc. She has won a gold medal for "Crane" at KASHIPEX 2019, Varanasi, India organized by the Varanasi Head Post Office.



Hareram Birla

Dr. Hareram Birla completed his Doctoral degree from the Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, India in 2021. He has a keen interest in the role of medicinal herbs in neurodegenerative disorders. He has published many articles on the role of medicinal herbs in managing Parkinson's disease. Moreover, he was awarded the prestigious Brain Prize from FENS-IBRO in 2019 for outstanding work in the field of medicinal herb and cognitive science. He also received a fellowship from the Indian Academy of Science during his master's program. He is a member of various international and national societies of neuroscience. He is also a Bentham Science Ambassador and serves as a reviewer for many reputed journals. Recently, he joined Rutgers University, New Jersey, USA as a Postdoctoral Fellow.



Chetan Keswani

Dr. Chetan Keswani did his Ph.D. from the Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, India. Currently, he is the group leader in the Academy of Biology and Biotechnology, Southern Federal University, Rostov-on-Don, Russia. He has a keen interest in regulatory, commercialization, and intellectual property issues of microorganisms. He is an elected Fellow of the Linnaean Society of London, UK, and received the Best Ph.D. Thesis Award from the Uttar Pradesh Academy of Agricultural Sciences, India in 2015. He is an editorial board member of several reputed microbiology journals and received Springer-Society Award (2020) for Excellent contribution to the journal 'Environmental Sustainability', Outstanding Editor Award (2019) from the journal Archives of Phytopathology and Plant Protection, 'Top Reviewer Award (Agricultural Sciences)' from Publons in 2018. In addition, Dr. Keswani has edited ten volumes from leading publishers including CRC Press, Elsevier, Springer-Nature and CABI.