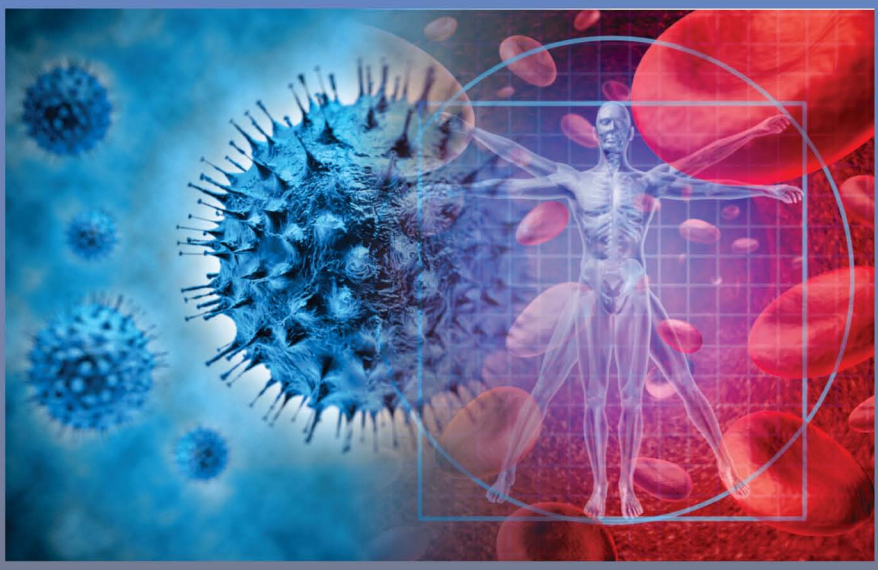
Holistic Approaches to INFECTIOUS DISEASES



Anne George • Joshy K. S. • Mathew Sebastian
Oluwatobi Samuel Oluwafemi • Sabu Thomas
Editors

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Anne George, MD
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Sabu Thomas, PhD

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ABOUT THE EDITORS

Anne George, MD
Associate Professor, Department of Anatomy, Government Medical College, Kottayam, India

Anne George, MD, is an Associate Professor at the Government Medical College, Kottayam, Kerala, India. She did her MBBS Bachelor of Medicine and her Bachelor of Surgery at Trivandrum Medical College, University of Kerala, India. She acquired a DGO (Diploma in Obstetrics and Gynaecology) from the University of Vienna, Austria; a Diploma of Acupuncture from the University of Vienna; and her MD from Kottayam Medical College, Mahatma Gandhi University, Kerala, India. She has organized several international conferences, is a fellow of the American Medical Society, and is a member of many international organizations. She has five publications to her name and has presented 25 papers.

Joshy K. S.

Joshy K. S., is a researcher working at the International and Inter University Centre for Nanoscience and Nanotechnology and C.M.S. College, Mahatma Gandhi University, Kottayam, Kerala, India. She has received a bachelor's degree in chemistry from Kerala University, Kerala, India; a master's degree in polymer chemistry from the School of Chemical Sciences Mahatma Gandhi University, Kottayam, Kerala, India; and an MPhil degree in polymer chemistry from Cochin University of Science and Technology, Kochi, Kerala, India. Joshy carried out her PhD work at Mahatma Gandhi University, Kottayam, Kerala, India. She is currently pursuing her research on the development of lipid and polymer nanoparticles for drug delivery applications. She has published in international journals and conference proceedings.

Mathew Sebastian, MD
Senior Consultant Surgeon, Elisabethinin Hospital, Klagenfurt, Austria; Austrian Association for Ayurveda

Mathew Sebastian, MD, has a degree in surgery (1976) with a specialization in Ayurveda. He holds several diplomas in acupuncture, neural therapy (pain therapy), manual therapy, and vascular diseases. He was a missionary doctor in Mugana Hospital, Bukoba in Tansania, Africa (1976–1978) and underwent surgical training in different hospitals in Austria, Germany, and India for more than 10 years. Since 2000 he has been the doctor in charge of the Ayurveda and Vein Clinic in Klagenfurt, Austria. At present he is a Consultant Surgeon at Privatclinic Maria Hilf, Klagenfurt. He is a member of the scientific advisory committee of the European Academy for Ayurveda, Birstein, Germany, and TAM advisory committee (Traditional Asian Medicine, Sector Ayurveda) of the Austrian Ministry for Health, Vienna. He conducted an International Ayurveda Congress in Klagenfurt, Austria, in 2010. He has several publications to his name.

Oluwatobi Samuel Oluwafemi, PhD
Senior Lecturer, Department of Chemistry and Chemical Technology, Walter Sisulu University, Mthatha Campus, Eastern Cape, South Africa

Oluwatobi Samuel Oluwafemi, PhD, is a Professor at the Department of Applied Chemistry, University of Johannesburg, South Africa. He has published many papers in internationally reviewed journals and has presented at several professional meetings. He is a fellow of many professional bodies and is a reviewer for many international journals, and he has received many awards for his excellent work in material research. His current research interests include green synthesis and application of nanoparticles in medicine, water treatment, polymer, LEDs, and sensors.

Sabu Thomas, PhD
Director, International and Inter University Centre for Nanoscience and Nanotechnology, Mahatma Gandhi University, Kottayam, Kerala, India

Dr. Sabu Thomas is a Professor at the School of Chemical Sciences and Honorary Director of the International and Inter University Centre for Nanoscience and Nanotechnology, Mahatma Gandhi University, Kottayam, Kerala, India. He joined Mahatma Gandhi University as a

full-time faculty in 1987. He has been associated with several universities in Europe, China, Malaysia, and South Africa. Professor Thomas is a member of the Royal Society of Chemistry of London, a member of the New York Academy of Science, USA, and the recipient of awards from the Chemical Research Society of India and the Material Research Society of India (2013). Professor Thomas has supervised 65 PhD theses, and he has more than 530 publications, 43 books, four patents, and 18163 citations to his credit. The h-index of Prof. Thomas is 68, and he is listed as the 5th position in the list of Most Productive Researchers in India in 2008. His research focuses on polymer blends, recyclability, reuse of waste plastics and rubbers, fiber-filled polymer blends, nanocomposites, elastomers, pervaporation phenomena, and sorption and diffusion.

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CONTENTS

LIST OF CONTRIBUTORS

Sana Aboobacker
Department of Pharmacology, Fr. Muller Medical College, Mangalore, Karnataka, India – 575002

Beena Antony
Fr. Muller Medical College, Mangalore, Karnataka, India – 575002

Mona Bakr
The National Institute for Laser Enhanced Sciences, Cairo University, Egypt

Samarth Bhatt
Jena University Hospital, Friedrich Schiller University, Institute of Human Genetics, Kollegiengasse 10, D-07743 Jena, Germany

Purna Chandra Dash
Health Economist, Team Leader, Conseil Sante, France

Tarek A. El-Tayeb
The National Institute for Laser Enhanced Sciences, Cairo University, Egypt

Mini Ghosh
School of Advanced Sciences, VIT University, Chennai Campus, India

Iman E. Gomaa
German University in Cairo, Egypt

Poonam Gupta
Molecular Virology Laboratory, Department of Biotechnology, Jamia Millia Islamia, New Delhi – 110025, India, E-mail: superm12@gmail.com

Mohammad Husain
Molecular Virology Laboratory, Department of Biotechnology, Jamia Millia Islamia, New Delhi – 110025, India, E-mail: mhusain2@jmi.ac.in

Mwiya Liamunga Imasiku
Department of Psychiatry, School of Medicine, University of Zambia, Lusaka, Zambia

Thomas Liehr
Jena University Hospital, Friedrich Schiller University, Institute of Human Genetics, Germany

R. Oviya
Department of Bioinformatics, Bharathiar University, Coimbatore – 641046, India

Princy Louis Palatty
Fr. Muller Medical College, Mangalore, Karnataka – 575002, India

P. Rajendran
Programme Director, PACT Programme, HLFPPT, Bhopal, India

R. Sathishkumar
Department of Biotechnology, Salem Sowdeswari College, Salem – 636010, India

M. Sharanya
Department of Bioinformatics, Bharathiar University, Coimbatore – 641046, India

Surya Pratap Singh
Department of Biochemistry, Banaras Hindu University, Varanasi, India

Srinadh
M&E Officer, PACT Programme, HLFPPT, Bhopal, India

Daniela Cristina Stefan
Department of Pediatrics and Child Health, Tygerberg Children's Hospital Stellenbosch University, Cape Town, South Africa

Susan Westfall
Department of Biochemistry, Banaras Hindu University, Varanasi, India; Department of Pharmaceutics, Faculty of Pharmacy, Babu Banarasi Das National Institute of Technology & Management, Lucknow – 227105, Uttar Pradesh, India

LIST OF ABBREVIATIONS

Aβ	amyloid beta
AD	Alzheimer's disease
ADL	actions of daily living
AIDS	acquired immune deficiency syndrome
ALL	acute lymphoblastic leukemia
APP	amyloid precursor protein
ART	antiretroviral treatment
ARVs	anti-retroviral drugs
BL	Burkitt lymphoma
BOR	bed occupancy rate
BSS	behavioral surveillance survey
BTR	bed turnover ratio
CAE	*Centella asiatica* extract
CBAs	carbohydrate-binding agents
CCC	community care centre
CCE	continued comprehensive education
CCR	chemokine coreceptor
CIN	cervical intraepithelial neoplasia
CMIS	computerized management information system
CMV	cytomegalovirus
CRFs	circulating recombinant forms
CRI	co-receptor inhibitor
CSF	colony-stimulating factors
CSSP	center for specialized studies and programs
DAR	drug adherence rate
DTC	diethyldithiocarbamate
EBV	Epstein Barr virus
ETC	electron transport chain
EWBS	existential well-being scale
FDA	Food and Drug Administration
FIs	fusion inhibitor
GNA	*galanthus nivalis* agglutinin
HAART	highly active antiretroviral therapy

HD	Huntington's disease
HHA	*hippeastrum* hybrid agglutinin
HIV	human immunodeficiency virus
HLFPPT	Hindustan Late Family Planning Promotion Trust
HPV	human papilloma virus
HSCs	hematopoietic stem cells
HSP	heat shock protein
HSV	herpes simplex virus
IDUs	intravenous drug users
IL-6	interleukin-6
INSTI	integrase strand transfer inhibitor
IRIS	immune reconstitution inflammatory syndrome
KS	Kaposi sarcoma
LED	light-emitting diode
mAb	monoclonal antibody
MDGs	millennium development goals
MFC	minimal fungicidal concentration
MFD	minimum fungicidal dilution
MIC	minimal inhibitory concentration
MID	minimum inhibitory dilution
MIS	management information system
MS	mass spectroscopy
MSM	men having sex with men
MVA	modified vaccinia virus Ankara
NACP	National Aids Control Program
NCI	National Cancer Institute
NFHS	National Family Health Survey
NHL	non-Hodgkins lymphoma
NIH	National Institutes of Health
NILES	National Institute for Laser Enhanced Sciences
NMR	nuclear magnetic resonance
NNRTIs	non-nucleoside reverse transcriptase inhibitors
NO	nitric oxide
NPs	nanoparticles
NtRTIs	nucleotide reverse transcriptase inhibitors
OH^-	hydroxyl radical
OIs	opportunistic infections
PACT	promoting access to care and treatment

PAF	platelet-activating factor
PBS	phosphate buffered saline
PCNSL	primary CNS lymphomas
PCP	*Pneumocystis jirovecii* pneumonia
PD	Parkinson's disease
PIs	protease inhibitors
PRM-A	Pradimic In a
QPRs	quarterly progress reports
RISC	RNA-induced silencing complex
ROS	reactive oxygen species
RWBS	religious wellbeing scale
SCC	squamous cell carcinoma
SDA	Sabourauds dextrose agar
SDAT	senile dementia of Alzheimer's type
siRNA	small interfering RNA
SIVs	simian immunodeficiency viruses
SR	sub-recipient
SWBS	spiritual well-being scale
TB	tubercle bacillus
TCM	traditional chinese medicine
TIs	targeted interventions
TMPMP	trimethoxy phenyl 1' methoxy propionaldehyde
TNF	tumor necrosis factor
UDA	*Urtica dioica* agglutinin
WHO	World Health Organization

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PREFACE

This book describes a holistic approach to the prevention and control of infectious diseases from enteric pathogens. Holistic approaches to infectious diseases deal with different concepts or approaches to take care of the challenging diseases. According to the World Health Organization reports, infectious and parasitic diseases are the second leading cause of death in the world, and the leading cause of infectious disease is due to the enteric pathogens and they cause almost two million deaths every year. The first four chapters of the book deal with different approaches such as ayurvedic, bioinformatic, fungal, and metal-based treatment to diseases. The remaining chapters fully focus on various approaches to HIV and AIDS—one of the most challenging infectious disease to mankind.

Ancient medical practices provide novel paradigms to understand chronic neurodegenerative diseases due to their unique outlook of disease pathology. Ayurveda is the ancient medical wisdom of India that provides novel and powerful insights for the preemptive and therapeutic treatment of neurodegenerative diseases. Ayurveda describes the disease pathology as being derived from the accumulation of *vata* or air in the brain. There are also traditional formulations composed of several herbs whose combined action against various aspects of the disease pathology effectively rescues the symptoms of the disease. It has been shown that natural therapies are equally or more effective than modern medicines with a longer efficacy and zero side effects.

Various microscopic organisms live harmlessly inside the body and on the surface of the skin. However, certain types of fungus that are normally harmless, on overgrowth, can cause superficial and systemic infections, which are more commonly seen in those people undertaking antibiotics, corticosteroids, immunosuppressant drugs and contraceptives. This also prevails in people with endocrine disorders, immune diseases, diabetes and others diseases, such as AIDS, tuberculosis, major burns and leukemia, especially, found in obese people with excessive skin folds.

Alternative medicine is an age-old tradition and a proven skill which is presently entering the mainstream, holding promises for combating various dreadful diseases in which our modern medicines have failed.

Though traditional medicine has been developed more by observation, practice and skill rather than scientific proven mechanism, still, the medicinal effectiveness is too broad and effective to be ignored. Recent advances in holistic medicinal research are towards uncovering the molecular mechanism of inhibition. Advances in biology and biotechnology have greatly improved our understanding of the human system and mode of drug-target interaction. To aid with these technologies, computational approaches termed bioinformatics play an important role. Genomics, proteomics, transcriptomics, data mining, text mining, network construction, expression studies, etc. are some areas of bioinformatics which when interconnected interpret various important information on the medical aspects and opens up challenges and solutions towards personalized medicine and drug discovery.

From Chapter 5 onwards the chapters concentrate on HIV and AIDS and its recent trends and treatment regimes, case studies, etc. The Acquired Immune Deficiency Syndrome (AIDS) is a deadly disease of the human immune system that is caused by infection with the human immunodeficiency virus (HIV). As per the current understanding of AIDS, in the initial stage of infection, a person experiences a brief period of influenza-like illness. Later in the subsequent stages, this is typically followed by a prolonged period without any significant symptoms. As the illness progresses, it interferes more and more with the immune system, making the person much more likely to get infections, including opportunistic infections OIs and tumors that do not usually affect people who have efficient working immune systems. Worldwide, about 33.2 million people live with AIDS and about 2.1 million AIDS-related deaths occur each year including 3,30,000 children. Though a breakthrough has been reported, so far there is no cure for AIDS, and this disease is endemic in many parts of the world and especially in sub-Saharan Africa. The old wisdom of 'prevention is better than cure' is truly applicable in the case of HIV/AIDS transmission. The most common HIV defining and related cancers in children are: Kaposi sarcoma (KS), Burkitt lymphoma (BL) and leyomyosarcoma (mainly in developed countries). Despite progress in the treatment and survival of childhood cancer globally, the need for adapted protocols and randomized trials for HIV-related malignancies in children remains a priority. The awareness and impact of HIV/AIDS is different in developed countries and developing countries. Various studies show that about 75% of infected people are aware of their HIV sero status in the USA

and Europe, while only 10–20% in Indians. There are many factors attributing to this, which include limited access to health care facilities by the population, lack of basic infrastructure for early diagnosis of HIV, which requires well-established laboratories, lack of funds to support awareness or preventive campaigns as well as the specific treatment like highly active antiretroviral therapy (HAART). As reported by certain investigators, the spectrum of OI and the prevailing HIV sero-status are expected to change as a result of HAART. Hence an early detection and diagnosis of OI may help in effective disease management. Antiretroviral therapy mainly consists of drugs that are capable of reducing the disease burden on the infected individuals and helps in preventing opportunistic infections that are often the cause of death among HIV patients. The groups of drugs range from entry inhibitors to maturation inhibitors, which aim at terminating the further development of HIV by acting at different stages of its life cycle.

The Government of India established a National AIDS Control Program (NACP) to combat the HIV epidemic. During NACP I (1992), there was increased awareness about HIV/AIDS, particularly among the urban population, and subsequent successful intervention programs and the strengthening of STDs clinics across the country were major achievements. During NACP II, the classification of states has focused on the vulnerability of states, with states being classified as high and moderate prevalence and high and moderate vulnerability. The primary goal of NACP III is to halt and reverse the epidemic in India over the next five years by integrating program for prevention, care, support and treatment. Community Care Centre (CCC) is a comprehensive facility-providing medical, counseling, referral and outreach service to the registered PLHIV. The overall goal of the program is to improve the survival and quality of life of people living with HIV/AIDS (PLHIV). Envisioned as a home away from home, CCC is a facility for providing accessible, affordable, and sustainable counseling, support, and treatment to PLHIV. With the medical services being an integral and important part of the program, CCCs have a critical role in helping PLHIV gain easy access to ART treatment and counseling on primary prevention, nutrition, drug adherence, etc. The main functions of these CCCs are to provide treatment to the registered PLHIV on various types of opportunistic infections/side effects, providing quality of counseling, providing home a based care through outreach component and LFU tracking as per the list given by ART Centers. Currently, 35 CCCs

are in functional among five states and one union territory of India. A total of 66,471 PLHIV were registered with the CCCs and availing various services till December 2012 for smooth implementation of the program. HLFPPT has been monitoring and providing constant technical support to the Community Care Centers (CCCs) scattered among the above-said states.

In this book, topics on new approaches to infectious diseases, recent trends in HIV AIDS, ongoing treatments, case studies and the major achievements of the Government against this deadly disease are discussed in a lucid manner, and these aspects are presented in a readily accessible form. Each chapter provides an in-depth array of knowledge satisfying persons related to this field like researchers, doctors, students and professionals.

—Sabu Thomas
Anne George
Mathew Sebastian
Oluwatobi Samuel Oluwafemi
Joshy K. S.

CHAPTER 1

THE AYURVEDIC TREATMENT OF NEURODEGENERATIVE DISEASES

SUSAN WESTFALL and SURYA PRATAP

CONTENTS

ABSTRACT

Ancient medical practices provide novel paradigms to understand chronic neurodegenerative diseases due to their unique outlook of disease pathology. Ayurveda is the ancient medical wisdom of India that gives novel and powerful insights for the preemptive and therapeutic treatment of neurodegenerative diseases. Ayurveda describes the disease pathology as being derived from the accumulation of *vata* or air in the brain. In general, treatments include both internal and external practices and herbal therapies to reduce the amount of air in the body in addition to stimulating the central nervous system (*medhya rasayanas*). There are also traditional formulations composed of several herbs whose combined action against various aspects of the disease pathology effectively rescues the symptoms of the disease. Due to the failure of modern allopathic medicine to effectively treat chronic neurodegenerative diseases, many people are turning to alternative natural therapies. It has been shown that natural therapies are equally or more effective than modern medicines with a longer efficacy and zero side effects. The following summarizes the latest research on a battery of Ayurvedic herbs that were traditionally used in the treatment of Parkinson's, Alzheimer's and Huntington's disease and the potential these herbs have to become modern therapies.

1.1 INTRODUCTION

1.1.1 AYURVEDA

Ayurveda is the ultimate holistic medical wisdom and literally means the 'wisdom of life' (*ayus* = life; *veda* = wisdom). It considers the body, mind and spirit to be a seamless system between which proper homeostasis and harmony is required to instill perfect health and a clear path to enlightenment. Health in Ayurveda means not only physical health but, more importantly, mental clarity. Health in Sanskrit is *svastha* which, when broken down means '*sva'* self and '*stha'* established. This self is purposely ambiguous in that it means both the physical 'self' connected to the ego and the higher, spiritual 'Self' that is connected with God. So 'health' in Ayurveda is defined as a proper establishment of self both physically (proper physical health) and mentally (mastery over indulgence, sensory cravings and separation from God). The ultimately goal of Ayurveda is to

achieve optimal physical health in order to have a clear path to God and enlightenment.

> *Ayurveda scrutinizes the subtle process of life, studies its nature, ways and conditions of development and deduces there-from a universal course of conduct for man's guidance in life.*
>
> —Ananthacharya (1939)

The God of Ayurveda, Lord *Dhanvantari*, is an avatar of the great Lord *Vishnu* and is known from the Vedas as a physician of the Gods. According to mythology, Lord *Dhanvantari* emerged from the churning of oceans by the *asuras* (demons) and *devas* (Gods) holding a goblet of *amrita*, the almighty nectar of immortality and spiritual enlightenment. Anyone seeking some grace of health will often pray to Lord *Dhavantari*.

In legend, it is said that Ayurveda originated at the base of the Himalayan mountains around 3000 BC during the period of the Indus Valley civilization. It is said that a congregation of the best medical *rishis* at the time convened there to discuss the pathology and treatment of many diseases under the divine guidance of Indra, the God of rain. Indra taught the medicine of the gods, Ayurveda to a missionary of the *rishi*s who since then spread the wisdom of Ayurveda through the generations by oral traditions. Ayurveda is so old that it is even mentioned in all of the four *Vedas*, the sacred texts of Hinduism. Ayurveda was practiced as a traditional medicine for thousands of years until it was finally written down by the master physicians of the time. Even today, the *Charak Samhita* and *Sushruta samhita* remain the ultimate references for Ayurveda, although there are many ancillary texts describing specific treatments using the wisdom of Ayurveda. Ayurveda, even at that time, was divided into eight different sub-specialties namely, *kayachikitsa* (internal medicine), *baala chikitsa* (pediatrics), *graha chikitsa* (demonology), *urdhvanga chikitsa* (diseases of head and neck), *shalya chikitsa* (surgery), *visha chikitsa* (toxicology), *jara chikitsa* (rejuvenation) and *vrsha chikitsa* (aphrodisiac therapy).

In Ayurveda, everything is said to be a unique composition of the five elements or the *pancha maha bhutas*, namely *prithvi* (earth), *aapas* (water), *vayu* (air), *tejas* (fire) and *aakash* (ether). The human body is born with an innate and unique cohort of these elements, which defines one's physical and mental qualities. Physically, the combination of the five elements is referred to as *doshas*, the biological humors. There are three *doshas: vata* (air and ether), *pitta* (fire and water) and *kapha* (earth and

water). *Doshas* have no physical bearing but reflect a person's physical tendencies, mental habits and predisposition to reacting to environmental stimuli. More simply, a person's *doshic* inheritance gives them certain physical and mental qualities (i.e., tall versus short, dry versus oily skin, shy versus rambunctious, focused versus aloof temperament, etc.). It is important to note that the *doshic* predisposition that every person is born with, known as *vikriti*, does not change throughout life. Thus, a *vata-pitta* person will always have a *vata-pitta* predisposition. However through life, exposure to unbalancing stimuli can create symptoms of excessive or depleted *doshas* and this state is called *vikriti*. Ultimately, everyone should strive to be a perfect balance of the three *doshas* thus avoids the weaknesses and embrace the strengths of each respective *dosha*.

Very briefly, a *vata* person will have particular characteristics, namely tall and lean with a dreamy and idealistic personality reflecting the elusiveness and changeability of the light air and ether elements. A *pitta* person will be naturally muscular, have a tendency to be hot with a fiery and determined attitude with a predisposition towards aggression. Finally, a *kapha* person will be more solid, slow and steady like their earth element and have a warm, loving and tenacious personality. (Please note that the categorization into a *doshic* type is very deep and these descriptions only barely touch the surface of what characterizes a *dosha*). Nevertheless, a person will be a combination of a defined proportion of each of these *doshas* and hence will have different propensities towards given attributes. This is an important consideration whenever a herb is prescribed to treat a specific disorder. For example, giving a highly heating herb to a person with a lot of internal fire (*pitta*) will disrupt their physiological homeostasis in the treatment of the *vikriti* or disease, likely rearing more disease and disruptions. Likewise, giving an extremely bitter herb to a predominantly *vata* individual will rear many imbalances in their constitution. In this light, the taste (*rasa*), properties (*virya*), qualities (*guna*) and effect of taste after digestion (*vipaka*) need to all be considered before indulging in any herbal treatment.

1.1.1.1 AYURVEDA IN NEURODEGENERATION

One branch of Ayurveda defines the potency of a class of herbs known as the *rasayan chikitsas,* literally 'rejuvenative medicines'. Plants that are

considered *rasayan'*s are whole-body tonics that stimulate immunity and metabolism and promote health and longevity by optimization of homeostatic processes (Auddy et al., 2003). Such herbs stimulate happiness, youthfulness, divine connectedness and act as tonics for young, middle-aged and elderly alike. Chemically, the magic of these herbs has been postulated to be due to their high content of antioxidants (Sharma et al., 1992), which battle many of the acquired diseases from daily stress, age and environmental toxins. But, not all *rasayan*'s are created equal. There are specific *rasayan*'s that are more adept for targeting particular areas of the body. Of particular interest are the *medhya rasayan*'s, the rejuvenators of the brain. These *rasayan*'s are particularly adept at boosting memory, preventing cognitive deficits and improving overall brain function. From the ancient literature, the most important *medhya rasayan*'s, or nervine tonics, are (in order) Ashwagandha, Brahmi, Jatamansi, Jyotishmati, Mandukparni, Shankhapushpi and Vacha (Ven Murthy et al., 2010).

One of the original Ayurvedic formulations acting as a nervine tonic was actually designed against Parkinson's disease. This mixture contained a mixture of powdered *Hyoscyamus reticulatus* and *Mucuna pruriens* seeds together with *Withania somnifera* and *Sida cordifolia* roots prepared in cow's milk. In a recent clinical trial, the above mixture was administered to 18 clinically diagnosed Parkinsonian patients for 8 weeks and an extensive analysis on their symptomatic improvements was assessed (Nadashayana et al., 2000). This study indicated a significant improvement in the actions of daily living (ADL), motor tasks and an overall improvement in terms of the universal scale of Parkinsonian symptoms, the UPDRS rating. Tremors were reduced and the onset of bradykinesia eradicated. This study attributed the anti-parkinsonian effects to the 200 mg of L-DOPA (the precursor to dopamine) found in each powdered dose, however more recent developments have indicated that there are many other components that can also contribute to its anti-Parkinsonian effects (Katzenschlager et al., 2004; Manyam et al., 2004).

More interestingly, this study went further into the essence of holistic Ayurvedic medicine and included a group of patients who received both the palliative treatment together with traditional cleansing (*panchakarma*) before the onset of treatment. It was found that prior cleansing further enhanced the motor benefits of the palliative treatments and the patients showed a heightened improvement in their ADL and UPDRS scores. The latter indices were only mildly improved in the groups taking the palliative

treatments alone. So together, it is not just the active ingredients of the herbs that contribute to the power of Ayurveda, but rather, the entire Ayurvedic paradigm of treating disease (Nadashayana et al., 2000).

1.1.2 NEURODEGENERATION

Neurodegeneration is probably the most feared condition in aging persons. The toll on one's health and family and the level of suffering is incalculable as this voracious disorder silently infects the mental processing of one's most cherished faculty: the brain. There are no treatments, limited understanding and an overall helplessness among doctors and the society to treat aging persons afflicted with this disorder. The economic burden in the US for treating Alzheimer's disease alone supersedes $100 billion per year. Thus, neurodegeneration is not only a personal problem, but also a societal problem and challenge for politicians and scientists alike.

Neurodegeneration is the progressive loss of neurons due to structural, molecular and functional damage eventually leading to cell death. The main causes of neurodegeneration are age, polyglutamine accumulation, oxidative stress, protein aggregation (proteinopathies) and mitochondrial damage. Of these, the accumulation of oxidative stress from ageing, mitochondrial damage and environmental toxins are the biggest risk factors for neurodegeneration. Thus there is no surprise that the majority of neurodegenerative diseases have been attributed to an accumulation of oxidative stress. In such a pro-oxidative state, there is progressive damage of cells at the subcellular level eventually leading to cell death through apoptosis (programmed cell death), autophagy or if the damage is severe, necrosis (Scartezzini and Speroni, 2000).

1.1.2.1 OXIDATIVE DAMAGE AS A MAIN CAUSE OF NEURODEGENERATION

Every second of everyday in every cell of the body, a variety of oxygen free radicals collectively known as reactive oxygen species (ROS) are being produced. These little oxidative particles wreak havoc throughout the body by inflicting damage on tissues, cellular molecules and DNA. Oxidative damage is so pinnacle to age-related cognitive decline that even dietary regimes enriched in antioxidants have been associated with some

level of protection against neurodegenerative decline (Checkoway et al., 2002; de Rijk et al., 1997; Commenges et al., 2000).

ROS are created as the byproduct of normal biological processes, namely the energy producing process in mitochondria known as oxidative phosphorylation. During this process, electrons are passed between three subunits (I, II and III) of the 'electron transport chain' (ETC), which through a series of biochemical interactions, convert the energy of the electron ions into usable cellular energy. When there is damage or stress upon this delicate chain, the free electrons react erroneously with neutral molecules or become converted by enzymes into other dangerous counterparts. Most commonly, the free electrons will react with the abundantly present and electron-receiving oxygen molecules, hence the name reactive *oxygen* species. In this highly unstable state, oxygen becomes dangerous as it converts into a free radical: an atom, molecule or ion that has unpaired electrons thus existing in a highly unstable form.

ROS invoke damage by interacting with healthy or normal molecules, transferring to them a free electron and making these molecules themselves highly reactive. By far, the most reactive ROS is the hydroxyl radical (OH^-) as it reacts with everything from proteins, to lipids, to DNA to RNA. Ultimately, these molecules will promote damage throughout the cell by propagating a chain reaction of irrevocable damage and eventually cell death.

Age is the prime incident factor for the development of ROS. When we are young, our body still has a grand repertoire of antioxidant mechanisms that are fully functional and constantly protecting our cells against such damage. As we age however, these mechanisms become less and less functional and oxidative damage accumulates. For example, many of the enzymes present to protect the body from oxidants begin to lose functionality such as catalase, glutathione peroxidase and superoxide dismutase. Normally these enzymes take free radicals and metabolize them into harmless products, though when they become less functional with age, free radicals are not metabolized and accumulate proportionally in cells.

Environmental toxins are another main contributor to oxidative stress. Toxins such as herbicides, industrial fumes and synthetic food additives all tip the homeostatic balance of the body towards a pro-oxidative state. Such toxins can works through many mechanisms such as introducing new oxidative particles into the body, inhibiting antioxidant enzymes or

invoking mitochondrial damage thus increasing the production of free radicals (Halliwell, 2011).

It is not surprising then to acknowledge that the most important and common link between all neurodegenerative diseases is the induction of a pro-oxidant state. As it was mentioned, the incorporation of antioxidants into one's diet is enough to reduce the risk of developing neurodegenerative disease. But, what if we go further with this idea? Why not incorporate the most powerful antioxidants into the diet and lifestyle routines to greatly reduce the risk of developing any sort of disease? Indeed, herbal products and medicines outlined by traditional medicines allow just this. Many of the herbal medicines utilized in alternative medical techniques, including Ayurveda, are rich in polyphenols: chemical structures resembling a ring that are known to scavenger those damaging free radicals. Hence, the fight against neurodegeneration can start (and end) with the educated intake of Ayurvedic herbal medicines aimed to protect neurons against age- and environmentally-provoked oxidative damage.

Below is a description of the three most devastating neurodegenerative diseases, Alzheimer's disease, Parkinson's disease and Huntington's disease, and how oxidative damage plays a major role in each of their pathologies.

1.1.2.2 ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease facing society today and its main symptoms are progressive short-term memory loss and dementia, which eventually lead to death. Presently, it is estimated that 10% of the population over 60 and 50% over 80 are suffering from AD (Potter, 2013). In light of the rapidly ageing population, the number of cases is expected to quadruple by 2050. The symptoms of AD are severe, beginning with memory loss for recent events and escalating to confusion, aggression, irritability and retroactive memory loss (i.e., forgetting your friends, family and childhood events). Ultimately, the body begins to 'forget' how to preform autonomic functions as the motor systems begin to fail. The heart will stop beating, brain functions will be lost and eventually the patient will die. The severity of the debility and the looming increase in AD prevalence demands preventative measures for the global population.

The cause of AD is unknown. A small fraction of AD cases are familial or early-onset (10–15%) (Alzheimer's Association) and have been associated with mutations in amyloid precursor protein (APP), presenilin 1 and presenilin 2 (Sehgai et al., 2012). The majority of AD cases is sporadic in nature and are correlated with inheritance of the APO?4 allele, an inefficient form of APP. In all of these cases, the improper functioning of APP results in the inefficient breakdown of the beta amyloid protein, thus precipitating of the toxic version of amyloid beta (Aβ) protein, which is more prone to form the Aβ plaques characteristic of AD (Hardy and Higgins, 1992). In addition, there is a high prevalence of aggregated hyperphosphorylated tau proteins known as neurofibrillary tangles or senile plaques (Thompson and Vinters, 2012). Through not fully understood mechanisms, the accumulation of these plaques and tangles leads to the progressive and irreversible loss of neurons, mainly in the cortex and hippocampus (Tundo et al., 2012). It is believes that through the induction of apoptosis, activation of transcription factors and mitochondrial damage, these plaques induce cell death (Ramasamy et al., 2006).

There is another hypothesis regarding the etiology of AD, and this involves the loss of cholinergic neurons. Indeed, one of the earliest neurochemical signs of AD is the loss of cholinergic neurons (Bartus et al., 1982). Indeed, the depletion of acetylcholine in the brain is proposed to have a prominent role in the memory impairments of AD patients (Lahiri et al., 2004; White and Rusje, 2002). Although the evidence of this effect has become controversial, most of the drugs used to treat the symptoms of AD target the deficiencies in the cholinergic system.

Oxidative stress is also a risk factor for the development of AD (Butterfield et al., 2004) and studies have indicated clear markers of oxidative damage in AD brains (Pratico et al., 2000). Indeed increases in lipid peroxidation, protein oxidation and DNA oxidation have all been reported in AD patients and as shown in animal models, induction of antioxidantive mechanisms attenuates AD's progression (Zandi et al., 2004). Some believe that the mechanism of Aβ-induced cell death even may be aggravated by oxidative pathways (Cai et al., 2011). Actually, there is a direct correlation between the concentration of the hydroxyl ion and the co-localization of the hyperphosphorylated form of tau (Takeda et al., 2000). Further, oxidative damage plays a role in cytoskeletal abnormalities, a major pathological feature in AD (Smith et al., 1995). Clearly, many of the pathological pathways involved in the development of AD are

aggravated by oxidative stress and this very observation indicates strongly a role for herbal medicines with their potent antioxidant activity for the treatment of AD.

1.1.2.3 PARKINSON'S DISEASE

Parkinson's disease (PD) does not discriminate between race, religion or culture and affects 2% of people over 60 and 5% over 80 worldwide (Lees et al., 2009). It is characterized by the progressive degeneration of dopaminergic neurons in the *substantia nigra*, a midbrain region. The atrophy of these neurons is thought to contribute to the progressive motor deficits characteristic of PD. These symptoms include progressive shaking, slowness in movement, rigidity, depression, dementia and digestive difficulties. PD is a multifactorial disease instigated by both environmental and genetic factors. The etiology of PD remains debatable, though it is believed that the increase in oxidant stress in the brain from aging provokes the progressive degeneration of dopaminergic neurons. This effect can be aggravated by genetic factors, damaged mitochondria and the accumulation of ?-synuclein or Lewy bodies in corresponding brain regions.

Much research has been conducted to discern the precise mechanisms underlying PD, though the causes are diverse and still debated. The majority of PD cases are sporadic with a small percentage being due to genetic factors (1–5%). Several environmental toxins have been identified that increase the risk of PD development, namely the commonly used pesticides and herbicides such as paraquat, rotenone and MPTP. Nevertheless, both the environmental and genetic causes of PD have been found to act through similar mechanisms, the major one being oxidative stress (Tsang and Chung, 2009). Notably, the overproduction of ROS that has been noted in PD patients has been deemed to be a major cause of dopaminergic degradation in PD patients (Danielson and Andersen, 2008). Mitochondrial damage and the accumulation of the aggregated ?-synuclein protein are also important considerations for the degradation of dopaminergic neurons. For example, environmental toxins such as MPTP, paraquat and rotenone all inhibit complexes in the ETC leading to mitochondrial damage. Such damage increases the production of ROS as free electrons being shuttled through the ETC erroneously and at a higher frequency react with biological molecules.

The genetic and environmental risk factors not only increase the production of ROS, but also decrease the processivity of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase. Finally, the peroxidation of polyunsaturated fatty acids in the neuronal cell membranes (lipid peroxidation) rears a significant source of oxidative stress in models of PD. This initial oxidative damage begins a chain reaction creating many downstream degradation products that are harmful to the neurons (Dexter et al., 1989). Already the antioxidant defenses in neurons is compromised due to their weak defenses, so the further depletion of their potency severely lessens the ability of cells to defend themselves against the onslaught of oxidative stressors.

1.1.2.4 HUNTINGTON'S DISEASE

The pathogenesis of Huntington's disease (HD) is slightly different from AD and PD. HD affects 4 – 10 in 100 000 persons, primarily of Caucasian origin (Sandhir et al., 2013). HD is characterized by a spectrum of cognitive, psychiatric and motor symptoms such as chorea (jerky, uncontrollable movements) and poor coordination. In more advanced stages, HD patients will experience dementia and further complications of the motor deficits namely pneumonia and heart disease. Normally, these symptoms will begin later in life, between 35 and 44 years of age and due to the progression of symptoms, death will ensue about 20 years after symptoms begin. As there is largely a motor deficit and atrophy in the striatum of the post-mortem brains, this area has become the focus of the disease's pathology (Walker et al., 2010).

It is known that the mitochondria play a large role pathogenesis of this disease. Indeed, 3-nitropropoonic acid (3-NP) serves as a good model of HD as it is a neurotoxin that induces a loss of mitochondrial function by selectively inhibiting the activity of Complex II of the ETC (Gould et al., 1995). Similar then to AD and PS, this toxin increases the ROS production in the striatum eliciting HD-like symptoms (Bogdanov et al., 1998).

HD is caused by an autosomal dominent mutation in the Huntingtin gene, namely a series of 'CAG' triplet repeats. CAG encodes for the amino acid glutamine and when the protein of this gene is created, the extra glutamine residues invoke a dominent pathology in a number of ways. The number of CAG repeats in a sufferer of PD varies between individuals,