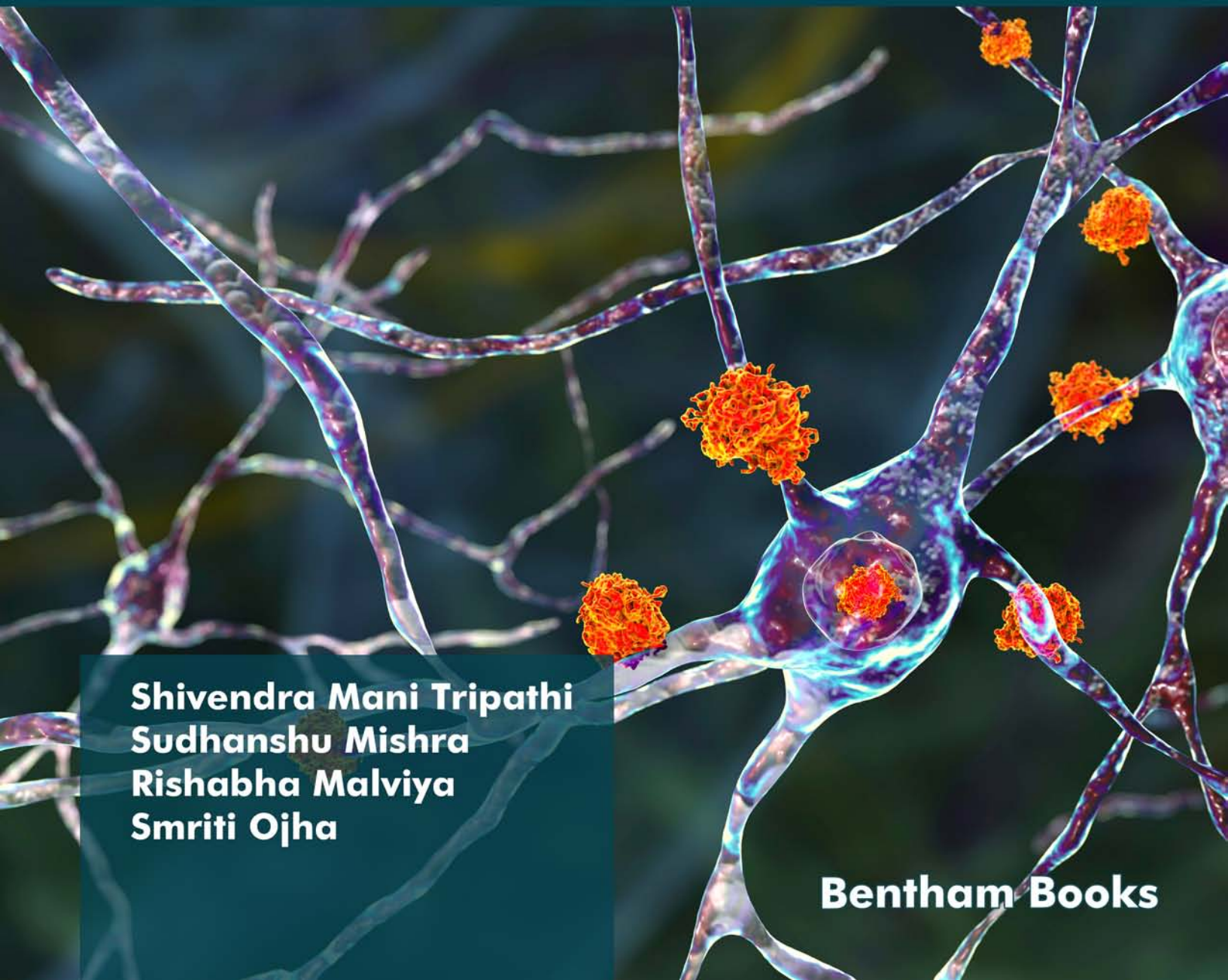
BIOACTIVE COMPOUNDS TARGETING NEURODEGENERATIVE DISEASES



Shivendra Mani Tripathi
Sudhanshu Mishra
Rishabha Malviya
Smriti Ojha

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Bioactive Compounds Targeting Neurodegenerative Diseases

Authored by

Shivendra Mani Tripathi
Faculty of Pharmaceutical Sciences
Mahayogi Gorakhnath University Gorakhpur
Uttar Pradesh
India

Sudhanshu Mishra
Faculty of Pharmaceutical Sciences
Mahayogi Gorakhnath University Gorakhpur
Uttar Pradesh
India

Rishabha Malviya
Department of Pharmacy
School of Medical and Allied Sciences
Galgotias University, Greater Noida
Uttar Pradesh, India

&

Smriti Ojha
Department of Pharmaceutical Science
& Technology, Madan Mohan Malaviya
University of Technology, Gorakhpur
Uttar Pradesh, India

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Authors: Shivendra Mani Tripathi, Sudhanshu Mishra, Rishabha Malviya, Smriti Ojha

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FOREWORD

This book is an invaluable resource that presents information about neurodegeneration, pathophysiology, and the management aspects of "Bioactive compounds for neurodegenerative diseases", authored by Mr. Sudhanshu Mishra and his team. The book chapters, which were written by a varied group of experts in the field, researchers, and professionals, cover a wide range of subjects, including various approaches to disease management, natural biomolecules, and their role in managing disease progression.

Students, researchers, and neurologists who are interested in the subject matter are the intended audience for the book. The book inspires readers to indulge in the knowledge about neurodegeneration, participate in conversations, and spread the word.

Bringing out a current peer-reviewed collection under the title "Bioactive compounds for neurodegenerative diseases " with contributors spanning across the world has been expertly done by the editors. It is quite amazing to see how the editors have attempted to encompass such a broad and dynamic subject in several engrossing pieces that shed light on the role of bioactive compounds in disease management. Enthusiastic readers will be captivated by the appealing pictures that illustrate intricate theoretical and experimental aspects as well as the overall production design. This book's goal is to document and explore advancements in both the diagnosis and possible treatment of NDDs using tried-and-true methods. It brings together scientists from all over the world with varying specialties and areas of interest in science to concentrate on NDDs.

It gives me great pleasure to provide the foreword for this esteemed, multi-authored, internationally peer-reviewed publication on a subject extremely important for the well-being of all. I hope the editors have a prosperous future and would love to see this modest start become a regular series. My heartfelt gratitude goes out to every contributor for their outstanding work in making this book a success.

With best wishes

Rohit Kumar Verma
International Medical University, Malaysia

PREFACE

We are thrilled to introduce our readers to the book "Bioactive Compounds Targeting Neurodegenerative Diseases." This comprehensive work is the culmination of extensive research efforts aimed at providing researchers and healthcare professionals with a valuable resource to address the challenges posed by neurodegenerative diseases.

Neurodegenerative diseases have long been a significant concern, and as our understanding of these conditions evolves, so does our approach to combating them. This book aims to bridge the gap between knowledge and action by empowering readers with the information they need to effectively manage and combat neurodegenerative diseases.

Each of the upcoming chapters delves into different aspects of neurodegenerative diseases, from the underlying mechanisms to the latest advancements in treatment strategies along with the challenges and intellectual properties. With the insights provided in this book, readers will be better equipped to engage in informed discussions with healthcare providers, make sound decisions, and take proactive steps toward managing neurodegenerative diseases.

This book is not only intended for researchers and healthcare professionals but also for caregivers, patients, and anyone seeking to understand and support those affected by neurodegenerative diseases. By fostering constructive dialogue and collaboration, this book catalyzes collective efforts to combat these challenging conditions. We trust that this book will serve as a trusted companion in the quest for improved treatments and outcomes for neurodegenerative diseases, inspiring readers to play an active role in promoting brain health and well-being.

Shivendra Mani Tripathi
Shivendra Mani Tripathi
Faculty of Pharmaceutical Sciences
Mahayogi Gorakhnath University Gorakhpur
Uttar Pradesh
India

Sudhanshu Mishra
Faculty of Pharmaceutical Sciences
Mahayogi Gorakhnath University Gorakhpur
Uttar Pradesh
India

Rishabha Malviya
Department of Pharmacy
School of Medical and Allied Sciences
Galgotias University, Greater Noida
Uttar Pradesh, India

&

Smriti Ojha
Department of Pharmaceutical Science
& Technology, Madan Mohan Malaviya
University of Technology, Gorakhpur
Uttar Pradesh, India

CHAPTER 1

Overview of Bioactive Compounds for Neurodegenerative Disorders

Abstract: The term “neurodegenerative disorders” refers to a broad category of pathological ailments that occur from increasing damage to the connections between the nervous system and the neurons. These disorders primarily affect neuronal malfunction and cause issues with strength, mobility, cognition, coordination, and sensation. Because of the body's need for and use of oxygen, the brain is susceptible to a variety of challenges, most notably oxidative stress. Potential neuroprotective drugs for the treatment of neurodegenerative disorders have been identified in natural products. Natural products derived from plants, animals, and fungi as well as the bioactive compounds they contain have been thoroughly investigated and studied in recent years for potential therapeutic uses against a range of disorders, including cancer, diabetes, hypertension, cardiovascular disease, and neurodegenerative diseases. The body's need for and usage of oxygen can lead to oxidative stress, which is one of the stresses that can affect the brain. The brain's high content of unsaturated fatty acids makes it more vulnerable. Crucial goals include addressing oxidative damage and developing effective and safe therapies for neurodegenerative diseases. Research into bioactive chemicals is essential to this endeavor.

Keywords: Bioactive compound, Hypertension, Neurodegenerative disorder, Natural compound, Oxidative stress.

INTRODUCTION

The term “neurodegenerative disorders” refers to a broad category of pathological ailments that occur from increasing damage to the connections between the nervous system and the neurons. The body's need for and use of oxygen makes the brain susceptible to a variety of challenges, most notably oxidative stress [1, 2]. The brain's high content of unsaturated fatty acids makes it more vulnerable. Pathogenesis establishes the parameters of typical pathogenic processes, of which apoptosis, oxidative stress, excitotoxicity, and conformational changes in neuronal proteins are of utmost relevance [3]. NDDs have no known effective medical treatment, and the existing strategy for managing these conditions has only been able to partially eliminate their clinical symptoms [4]. There are lots of potential

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outcomes in the investigation for natural compounds having bioactivity, and possessing various therapeutic properties like anti-inflammatory, anti-oxidant, and anti-tumorigenic activities, despite some recent advancements in chemical drug development [5]. In reaction to a severe insult traumatic event or ischemic brain damage, nerve cells are injured and mostly die, a condition known as acute neurodegeneration. The strong antioxidant and anti-inflammatory properties of naturally occurring bioactive substances make them interesting since they have many benefits for brain health [6].

Since long, natural products have been used and recognized for their therapeutic benefits. Phytoconstituents have been the subject of extensive research and exploration in recent years [7]. Numerous research works conducted in recent decades have documented the preventive properties of bioactive components against a range of disorders, including cancer, diabetes, heart disease, and neurological disorders. Potential neuroprotective drugs for the treatment of neurodegenerative disorders have been identified and evaluated for their therapeutic benefits in natural products [8].

Neurodegenerative Diseases

A variety of disorders known as neurodegenerative diseases (Fig. **1**) (NDD) are distinguished by continuing loss and selective malfunctioning of neurons and neural networks in the brain and spinal cord [9]. As a result, they can lead to a variety of issues, such as those involving mobility (known as ataxias), mental function (known as dementias), and the capacity to breathe, speak, and move. The aging of the world's population contributes to the rise in the prevalence of NDDs, which are crippling and incurable disorders [10]. Because the brain regulates several bodily functions, neurodegenerative diseases impact a variety of aspects of human functioning and impair the capacity to carry out both simple and complex tasks [11]. While in some cases, treatments aim to ameliorate symptoms, relieve pain if it is present, and/or restore movement and balance, most NDs develop without remission [12]. Neurodegenerative disorders are diverse ailments that cause neurons, glial cells, and their networks in the human brain and spinal cord to selectively malfunction and gradually lose their function [13]. Progressive loss of specific vulnerable neuronal populations is a hallmark of neurodegenerative disorders; this is in contrast to select static neuronal loss resulting from metabolic or toxic disorders [14]. Research has identified several similar processes *via* which dementia occurs, including the buildup of insoluble protein aggregates, apoptosis, necrosis, excitotoxicity, and neuroinflammation, despite the wide range of causes of neurodegenerative disorders [15]. Neurodegeneration is also influenced by downstream oxidative stress, decreased autophagy/lysosomal activity, and dysfunctional mitochondria [16, 17].

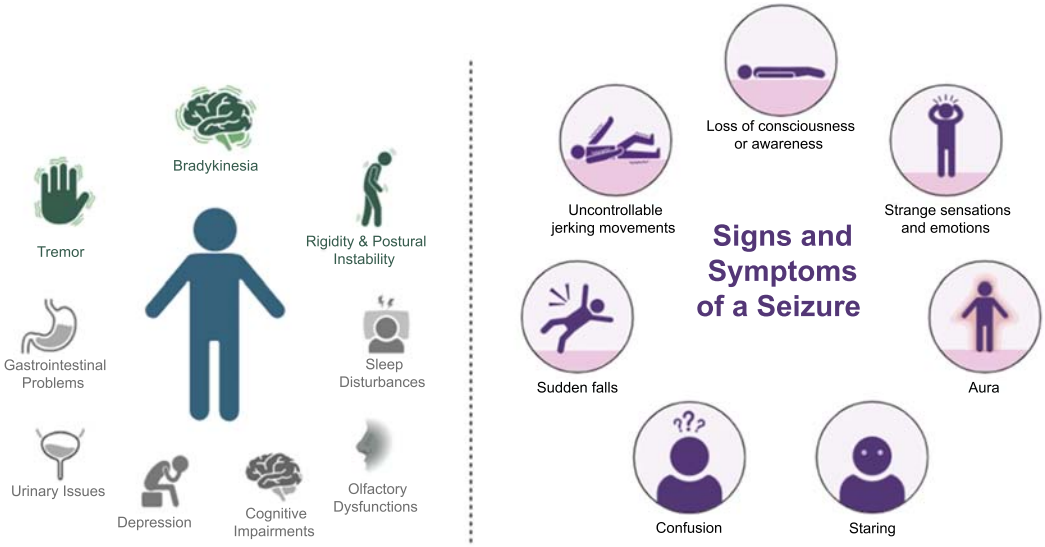

Fig. (1). Signs and symptoms of some neurological disorders.

Alzheimer's Disease (AD) and other Dementias

It is believed that the aberrant accumulation of proteins in and around brain cells is what causes Alzheimer's disease. Neurofibrillary tangles (NFTs), which are made of hyperphosphorylated tau protein, and amyloid-β plaques are the main causes of Alzheimer's disease (AD), a progressive neurodegenerative illness [18]. In addition to environmental and lifestyle variables including age and head trauma, genetic factors like mutations in the APP and PSEN genes and the APOE ε4 allele also play a part in the development of AD [19]. While tau tangles hinder neuronal transport and cause cell death, amyloid-β buildup impairs synaptic function and causes neuroinflammation. Cognitive decline is the result of neuronal loss, particularly in regions such as the hippocampus [20]. Other characteristics include cerebral amyloid angiopathy, astrogliosis, neuropil threads, and dystrophic neurites. These conditions work together to cause vascular dysfunction, brain shrinkage, and the gradual loss of memory, behavior, and cognitive functions in AD [21]. Furthermore, AD is associated with neuropil threads, dystrophic neurites, associated astrogliosis, microglial activation, and cerebral amyloid angiopathy [22].

Parkinson's Disease

The loss of dopaminergic neurons in the substantia nigra, a part of the brain involved in motor coordination, is the main cause of Parkinson's disease (PD), a progressive neurodegenerative illness [23]. Although the precise etiology is still unknown, environmental variables including age, pesticide exposure, and head

CHAPTER 2

Medicinal Plants and Their Phytoconstituents in Neurodegenerative Disorders

Abstract: The human brain is made up of neurons and neuroglia, the latter of which are essential for maintaining neurons and responding to injury. Brain activity impairment can result from malfunctioning neuroglia. Chronic neuroglial activation affects neurodegeneration, which has a major impact on brain aging and neuropathological diseases. There are intriguing neuroprotective chemicals in traditional medicine that may offer an effective option than synthetic drugs. Researchers can improve natural treatments for neurological disorders by isolating active phytochemicals while discovering more about their processes, doses, and safety profiles. A variety of food sources including marine algae have neuroprotective properties. Bioactive substances with anti-inflammatory and antioxidant properties are found in marine algae. Nuts, fruits, vegetables, and other foods include phytochemicals that can prevent neurodegeneration. Resveratrol, curcumin, sulforaphane, flavonoids, and organosulfur compounds are important substances that shield neurons by a variety of mechanisms, such as anti-inflammatory and antioxidant ones. In addition to supporting general brain health, a varied diet high in these neuroprotective chemicals may lower the risk of neurological disorders.

Keywords: Brain aging, Flavonoids, Human brain, Phytochemicals, Resveratrol.

INTRODUCTION

Neurons and neuroglia make up the extraordinarily complex structure of the human brain, with neurons being the primary source of nerve signal transmission [1]. Astrocytes and microglia are crucial for maintaining neurons and stepping in when they are harmed or under stress [2]. These neuroglia serve as watchdogs over the health of the neurons, and when they malfunction, it can seriously impair brain activity. Neuronal signals play a major role in neuroglial activation [3]. Acute injuries trigger responses that either aid in regenerating injured neurons or kill them if they are not viable; these responses are regarded as normal and neuroprotective. Chronic processes, however, have the potential to cause persistent neuroglial activation, which would impair their capacity to maintain homeostasis and possibly harm healthy neurons [4].

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An essential component of neuropathological disorders and brain aging is neurodegeneration. Brain pathology, which includes neurodegenerative and cerebrovascular illnesses, is a leading cause of death and cognitive impairment worldwide. Many neuropsychiatric and neurodegenerative conditions can be extremely crippling, including Parkinson's disease, depression, and Alzheimer's disease [5]. An important field of study is neuroprotection, which attempts to protect the central nervous system from both acute injuries (such as stroke or trauma) and chronic neurodegenerative diseases. Due to the scarcity of available treatments, stroke and dementia present substantial obstacles. This has prompted research into the mechanisms of neuronal death and the development of novel therapeutic agents. In the end, strengthening neuroprotection techniques can lessen the effects of neurological conditions and enhance general brain health [6].

Medicinal plants include natural phytochemicals that are frequently thought to be less hazardous than synthetic medications. However, because traditional herbal remedies were traditionally made from raw materials, there are questions about the precise therapeutic effects, repeatability, modes of action, and identities of the active ingredients [7]. The focus of recent research has switched from researching these plants as a whole to separating and analyzing their constituent parts. It is essential to discover and characterize the active compounds found in medicinal plants for treating neurological illnesses. This methodology enables scientists to evaluate their possible therapeutic benefits, particularly in the treatment of neurodegenerative illnesses [8]. Scientists hope to gain a better understanding of the mechanisms of action, dosage requirements, and safety profiles of particular phytoconstituents by isolating and researching them (Table **1**). This targeted approach may lead to the development of more effective and reliable natural remedies for neurological disorders while minimizing potential side effects associated with whole-herb preparations [9].

Table 1. Various phytoconstituents and their pharmacological activities.

Sr. No.	Active Constituents	Activity	Refs.
1.	Ascorbic acid	Anti-oxidant	[79]
2.	Acacetin/flavanoid	Antiparkinson	[80]
3.	Apigenin	Alzheimer	[81]
4.	Quercetin	Alzheimer/Parkinson	[82]
5.	Resveratrol	Alzheimer	[83]
6.	Sulforaphane	Anti-inflammatory	[84]
7.	Silibinin	Ischemia	[85]

Neurodegenerative Diseases

Progressive conditions of the central nervous system (CNS) that also impact the peripheral nervous system are known as neurodegenerative diseases. Neurodegeneration is the result of a slow and cumulative loss of brain cells, which characterizes them. Free radicals are the main causes of this process, and Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) contribute significantly to it by producing them [10]. The development of different neurological disorders is also significantly influenced by neuroinflammatory processes. Over 600 neurological illnesses have been reported globally, according to the National Institute of Neurological Diseases and Stroke [11]. Anxiety encompasses mental, physical, emotional, and behavioral aspects of psychological and physiological states. It can interfere significantly with daily life, leading to apprehension about everyday events. Anxiety disorders include seven clinical conditions: Generalized Anxiety Disorder (GAD), Panic Disorder, Phobias, Agoraphobia, Social Anxiety Disorder (SAD), Obsessive-Compulsive Disorder (OCD), Post-Traumatic Stress Disorder (PTSD), and Separation Anxiety Disorder. Neurotransmitters such as dopamine, noradrenaline, serotonin, neuropeptides, neurosteroids, and cytokines play modulatory roles in anxiety states [12].

The neuropsychiatric disorder known as attention-deficit/hyperactivity disorder (ADHD) is characterized by symptoms like restlessness, mood fluctuations, disorganization, and difficulty focusing. It usually starts in childhood and lasts throughout adulthood [13]. Depression is characterized by a lowered mood and widespread unhappiness that can range from mild melancholy to complete agony. It is a prevalent emotional condition impacted by both environmental and biological variables [14]. According to the World Health Organization (WHO), depression is a major cause of morbidity and mortality, with an estimated 450 million individuals suffering from mental or behavioral disorders [15]. Depression is associated with structural alterations in neurons, including abnormalities in 5-HT and its receptors, dysfunction of the HPA axis, and decreased volume of the frontal cortex and hippocampus [16].

Conditions such as Alzheimer's disease (AD) and Parkinson's disease (PD) are classified as dementia. Parkinson's disease (PD) is a severe motor disorder characterized by bradykinesia, tremor, stiffness, and impaired balance as a result of dopaminergic neurons in the substantia nigra being lost [17]. Memory loss, cognitive impairment, and psychiatric problems are characteristics of AD [18].

About 50 million people worldwide suffer from epilepsy, a condition marked by recurrent seizures brought on by an overabundance of cerebral neuron discharge.

CHAPTER 3

Nano carriers Containing Bioactive Compounds for Targeting Neurodegenerative Disorders

Abstract: Neurodegenerative Disorders (NDs) are caused by a major loss of neurons both structurally and functionally. The current method of disease management has now encountered several side effects and also the progressive nature of NDs always evokes patients to switch to other drugs. The helpful impact of medicinal plants in these situations has been attributed to their demonstration through several cellular and molecular processes. Natural phytochemicals have served as a good and reliable resource for disease treatment and management. A few neuroprotective mechanisms of these phytochemicals include the reduction in inflammatory responses, the inhibition of pro-inflammatory cytokines' functional aspects, such as tumor growth, and the enhancement of antioxidant qualities. Prevention strategies of these phytoconstituents for NDs heavily rely on variations in transcription and transduction pathways. Aging is one of the main causes of NDs and disease progression, which are mostly brought on by protein loss, oxidative and inflammatory stress, environmental changes, and other factors. Neurodegenerative disorders can be treated with natural substances. Some of the therapeutic herbs for preventing NDs are ginseng, *Withania somnifera, Bacopa monnieri, ginkgo biloba*, and others.

Keywords: Bioactive compounds, *Bacopa monnieri*, Cytokines, Natural phytochemicals, *Withania somnifera*.

INTRODUCTION

Worldwide, NDs impact millions of individuals, and they arise due to a lack of functional mechanisms of nerve cells, which progressively and gradually result in the death of nerve cells of the sympathetic and parasympathetic nervous system [1]. The risk of acquiring a neurological disease as well as its progression increases significantly with aging. The rising average lifespan is also a possible factor that more people will suffer from NDs in the ensuing decades. We need to increase our knowledge of the factors that contribute to neurodegenerative disorders and create fresh strategies for both prevention and therapy [2]. In susceptible people, NDs are characterized by gradual neuronal loss. Important physiological processes such as oxidative stress, proteotoxic stress, neuroinflammation, and apoptosis led to neuronal dysfunction and eventual death

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[3]. Because of the subsequent immune-based activation of the central nervous system (CNS), NDs are thought to impose a substantial burden on the population and the healthcare system. Activating or modifying the immunogenic responses can aid in brain regeneration and repair [4]. Nevertheless, immune-mediated conditions like infections, immunological-mediated diseases, and neurodegeneration can also be brought on by immune activation. Over time neurodegeneration slowly but steadily progresses when neurons and axons in the central nervous system begin to die [5]. This causes abnormalities in cellular function and, ultimately, cell death. The following symptoms, which include a variety of deficits including poor memory, lack of coordination, and the total incapacity to carry out daily tasks necessary for leading a healthy lifestyle, appear throughout the degenerative phase. The four most prevalent disorders on the list of NDs are Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD) [6]. These disorders are highly correlated with rising age, compromised immunity, environmental circumstances, and the affected individual's genetic makeup.

By improving the delivery of drugs to the central nervous system, nano-formulations and nanoparticles such as liposomes, Solid Lipid Nanoparticles (SLNs), polymeric nanoparticles, and magnetic nanoparticles provide innovative approaches to treating neurological disorders. While SLNs offer superior stability and prolonged drug release, liposomes enhance drug stability and release [7].

Magnetic nanoparticles provide for precise, external field-guided targeting, whereas polymeric nanoparticles provide controlled release with targeted delivery. Stability, flexibility, and biocompatibility are still issues despite the various advantages [8].

Challenges to the intranasal delivery of drugs include patient compliance, fast mucociliary clearance, low drug bioavailability, and nasal anatomical variability. To maximize effectiveness, tactics including mucoadhesive agents, penetration enhancers, and sophisticated delivery systems are being developed. Innovative formulations, patient education, and customized technology for better therapy results are needed to overcome these challenges [9].

Natural remedies (Table **1**), particularly Chinese herbal remedies, have gained attention recently as potentially effective treatment options for AD because of their ability to target the disease on several different levels [10]. An essential biological barrier separating the CNS from the circulatory system is the Blood-Brain Barrier (BBB). The BBB can keep many drugs from entering the nervous system in addition to blocking poisons. According to reports, 98% of small-molecule drugs with neuroprotective properties are unable to penetrate this

biological barrier [11, 12]. Furthermore, if a phytochemical can permeate the BBB, a low solubility index in brain tissue is another challenge. In most cases, patients require an increased dosage to obtain sufficient drug plasma concentrations. Nevertheless, toxicity at large dosages could result in harm [13]. With the development of nanotechnology in recent years, scientists have discovered that drugs contained in nanoparticles can cross the BBB to reach the affected area, boosting the concentration of drugs in the nervous system and offering promising opportunities for better drug delivery [14]. The latest developments in the application of nanomaterials to the treatment of a variety of NDs and important functions of several natural substances, particularly Chinese herbal medicine-loaded nanoparticles may open up new avenues for the development of dosage forms for the condition in the future [15].

Table 1. Medicinal plants with therapeutic potential for management of neuro-degenerated disorder.

Disease	Medicinal Plant	Phytoconstituents	Bioactivity	Outcomes	Ref
Alzheimer's Disease	*Ginkgo biloba*	Flavonoids, terpenoids	Antioxidant, anti-inflammatory, neuroprotective	Improved memory, cognitive function	[16]
Parkinson's Disease	*Mucuna pruriens*	L-DOPA, flavonoids	Dopaminergic, antioxidant	Improved motor symptoms	[17]
Glaucoma	*Ginkgo biloba, Cannabis sativa (CBD)*	Flavonoids, cannabinoids	Neuroprotective, antioxidant	Reduced intraocular pressure, improved vision	[18]
Multiple Sclerosis	*Panax ginseng*	Ginsenosides	Anti-inflammatory, neuroprotective	Reduced relapse rate, improved symptoms	[19]
Friedreich's Ataxia	*Ginkgo biloba, Bacopa monnieri*	Flavonoids, bacosides	Neuroprotective, antioxidant	Improved motor coordination, quality of life	[20]
Prion Disease	*Curcuma longa (Turmeric)*	Curcuminoids	Antioxidant, anti-inflammatory	Reduced prion accumulation, improved cognitive function	[21]
Amyotrophic Lateral Sclerosis	*Withania somnifera*	Withanolides, alkaloids	Neuroprotective, anti-inflammatory	Improved motor function, quality of life	[22]
Motor Neuron Disease	*Rhodiola rosea*	Salidroside, flavonoids	Neuroprotective, antioxidant	Improved motor function, delayed disease progression	[23]

CHAPTER 4

Intranasal Administration for Targeting Neurodegenerative Disorders

Abstract: The Blood-Brain Barrier (BBB) limits the ability of therapeutic molecules to reach the brain following oral or parenteral administration. The nasal delivery system has the potential to be used for drug delivery due to its ease of administration and increased bioavailability. This approach to brain targeting has shown great promise and is useful in treating a range of illnesses linked to dysfunctional brain function. This, along with drug elimination and inactivation during the drug's journey in the systemic circulation and hepatic metabolism, reduces the effectiveness of treatment, necessitates high drug dosages, and frequently results in unfavorable side effects. The anatomical benefits of the nasal route, which allow for the direct delivery of drugs from the nasal cavity to the brain and avoid the blood-brain barrier, are the driving force behind this developing discipline. In addition to playing a significant role in the pathophysiology of neurodegenerative illnesses, oxidative stress can also play a significant role in the damage caused by cerebral ischemia and apoptosis. An interesting new development in medicine is the fascinating intersection of medicinal plants, their bioactive constituents, and nanotechnology, which has shown promise in the treatment of various NDDs. Drug concentration in the brain is increased through nose-to-brain delivery, which circumvents the blood-brain barrier and permits the direct movement of therapeutic molecules.

Keywords: Cerebellomedullary, Nose-to-Brain, Nanoemulsion, Nano phytomedicines.

INTRODUCTION

The field of phytomedicine also known as herbal medicine with therapeutic and healing properties, has been spurred by the growing interest in phytochemicals, that is, chemicals present in fruits, vegetables, nuts, grains, legumes, and other plant foods that have health-promoting effects. Research shows that plant medicine has been used since the conception of disease cure [1]. Even now, Chinese and Indian herbal medicine continues to impact Western medicine. Nonetheless, a return to phytomedicines has been observed in recent years because of their affordability, effectiveness, and reduced potential for adverse

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effects. Plant parts such as leaves, stems, bark, roots, and fruits can be utilized to stop, postpone, or reverse the symptoms of a wide range of illnesses [2].

Black tea, *Mucuna pruriens*, *Hibiscus asper* leaves, *Tinospora cordifolia*, sesame seed oil, and *Ginkgo biloba* are among the plants that have been reported to be beneficial in the treatment of various NDs. Numerous beneficial benefits on α-synuclein aggregation, oxidative stress, neuronal degeneration, mitochondrial dysfunction, and locomotor activity have been reported for these and other plants. Researchers studying NDs have been increasingly interested in polyphenols, which are compounds found in plants that have a variety of qualities such as antioxidant, anti-inflammatory, and antiapoptotic effects [3]. Curcumin, ellagic acid, quercetin, and sulforaphane are examples of polyphenols that have similar health benefits to the plants mentioned above. Though their pharmacokinetic qualities still require work, phytomedicines have the potential to be the treatment of choice for various NDs like Parkinson's disease [4]. Certain limitations, including instability, lipophilicity, and molecular size, explain why phytomedicines show promise *in vitro* but less efficacy *in vivo*. Furthermore, the BBB also lessens the *in vivo* efficacy of phytomedicines, which is a concern with many drugs used to treat NDs [5].

By closely controlling the movement of chemicals into the brain, the Blood-Brain Barrier (BBB) divides the central nervous system from the peripheral blood circulation system. It is composed of five different parts: pericytes, astrocyte foot processes, microglia, basement membrane, and endothelial cells of capillaries. Each of these elements contributes special qualities that help maintain the BBB's strict regulation [6]. The absence of fenestrations in endothelial cells restricts the diffusion of proteins and small molecules. Furthermore, the diffusion of compounds soluble in water is inhibited by the interendothelial junctions that exist between the epithelial cells. The BBB is in charge of eliminating waste and keeping the brain's equilibrium while serving as a barrier to keep infections and toxins out. Because of this, only around 2% of small-molecule drugs and even fewer large-molecule treatments can penetrate the blood-brain barrier and reach the brain. This poses a significant obstacle to medication delivery to the brain in the treatment of neurodegenerative illnesses like Parkinson's disease [7]. Therefore, it is critical to examine phytomedicines' poor pharmacokinetic qualities before employing them to treat NDs. This may be accomplished by using carriers like nanoplatforms, along with advanced formulation strategies, which may facilitate the entry of phytochemicals *via* the nose-to-brain route. Certain drugs' physicochemical characteristics prevent them from passing across the blood-brain barrier and from reaching subtherapeutic concentrations in the tissues they are intended to treat. In this regard, the intranasal route presents a viable means of delivering medication to the brain due to its distinct anatomical characteristics.

Specifically, methods based on nanoparticles have proven to have an exceptional ability to get over the difficulties posed by the intranasal route and generate drug accumulation in the brain without going through the system [8].

Nose-to-Brain Drug Delivery Pathway

The nasal-brain administration route has gained interest recently as a viable substitute for intracranial medication delivery. This is because the paths for drug transport from the nasal cavity to the brain are being investigated more thoroughly than in the past as studies on the physiological and neurological systems of the nasal brain are documented [9]. It has recently been suggested that a fresh target for neurological illnesses may be the nasal-brain lymphatic connection. As an appealing substitute for the conventional parenteral and oral methods for the direct delivery of drugs to the brain, intranasal administration has been proposed as a means of achieving high drug levels in the brain. Due to the nasal cavity's special anatomical features, drug delivery is minimally invasive, has a quick stimulation of action, and does not cause a hepatic first-pass effect [10].

In paracellular transport, the cells engaged in this process are called sustentacular cells, and the absorption happens slowly and without the use of energy, while transcellular transport happens across the sustentacular cells and only involves lipophilic medicines [11]. Absorption *via* the systemic route from the respiratory area and the olfactory zone of the nose straight into the brain is one of two important routes for targeting the brain *via* the intranasal route. When a formulation administered *via* the intranasal route comes into touch with the nasal mucosa, it bypasses the blood-brain barrier and enters the brain quickly [12]. Furthermore, the highly hydrophobic medication exhibits effective targeting ability because of its high partition coefficient value.

The nasal cavity receives blood flow from the maxillary, ophthalmic, and facial arteries, thus nasal mucosa is highly vascularized. As a result, drug molecules injected into nasal cavity veins can swiftly travel from the carotid artery to the brain, where they exhibit reverse transfer [13]. Administering drugs by intranasal method comes after the drugs' perivascular transit to the central nervous system. The olfactory region having an olfactory nerve is one of the main pathways for drug absorption. When the drugs are delivered by the intranasal route, they primarily target the brain *via* this channel. The olfactory area of the nose contains supporting cells along with olfactory receptor neurons. The ophthalmic division, maxillary division, and mandibular region of the trigeminal nerve are responsible for transmitting sensory data to the brain from the oral cavity, nasal cavity, eyelids, and cornea. This region collectively forms a trigeminal nerve pathway for drug absorption to the brain *via* the nasal route [14].

CHAPTER 5

Blood Brain Barrier and Nanotechnology for Neurodegenerative Disorders

Abstract: The Blood-Brain Barrier (BBB) is a highly selective semipermeable membrane that separates the circulating blood from the brain's extracellular fluid, ensuring CNS homeostasis and protecting the brain from harmful substances while allowing essential nutrients to pass. The BBB, composed of specialized endothelial cells connected by tight junctions, poses a significant challenge for drug delivery to the brain due to its restrictive nature. With the help of nanotechnology and the special qualities of nanomaterials such as their tiny size, biocompatibility, and capacity to increase blood circulation promising solutions to these problems remain. The structure and function of the Blood-Brain Barrier (BBB), the potential of nanotechnology for delivering drugs to the brain, and the application of different nanomaterials, such as polymeric, liposomal, dendrimer, and inorganic nanoparticles, in the treatment of neurological disorders are all covered in this study. Also, the neurotoxicity of nanomaterials and the therapeutic and neuroprotective potential of phytoconstituents are explained.

Keywords: Blood-Brain Barrier, CNS homeostasis, Endothelial cells, Nanomaterials.

INTRODUCTION

The Blood-Brain Barrier (BBB) is a crucial interface between the bloodstream and the brain that plays a vital role in maintaining the homeostasis of the Central Nervous System (CNS). It is a highly selective semipermeable membrane that separates the circulating blood from the brain's extracellular fluid, regulating the passage of molecules, ions, and cells into and out of the brain [1]. The BBB is essential for protecting the brain from harmful substances while allowing the passage of essential nutrients and molecules necessary for brain function. Being the tightest endothelium in the body, the BBB also represents the main impediment to drug delivery to the brain [2]. The vascular tree is comprised of arteries and arterioles, which deliver blood to the tissues, the capillary bed, which is essential for gas and nutrient exchange within tissues, and venules and veins, which drain blood from tissues [3]. Each segment has different properties depending on where they are in the vascular tree as well as which organ they vas-

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cularize. There are three main structural classes of capillaries [4]. Continuous no-fenestrated capillaries of the skin and lung are joined together by cellular junctions, have a complete Basement Membrane (BM), and lack fenestra (pores) in their plasma membrane. Continuous fenestrated vessels of the intestinal villi and endocrine glands have a similar continuous structure but contain diaphragmed fenestra throughout their membrane [5].

The advancement of nanotechnology *via* integrated, interdisciplinary efforts will lead to novel perspectives of how neural circuits work as well as methods for the diagnosis and treatment of brain disorders [6]. The shortcomings of existing methods for delivering drugs across the blood-brain barrier to the central nervous system make this particularly important [7]. The unique characteristics of nanomaterials, including their smaller size, biocompatibility, ability to extend blood circulation, and lack of toxicity, have been utilized to develop a novel delivery system that facilitates the effortless administration of therapeutic compounds to the brain [8]. Targeting particular and non-specific brain locations is the foundation of nanotechnology-mediated drug delivery systems [9].

Artificial Intelligence (AI) is advancing nanocarrier formulation for brain targeting *via* the nasal route by enabling predictive modeling and optimization of nanoparticle properties. AI tools, like machine learning algorithms, predict drug encapsulation efficiency, particle size, and biocompatibility, tailoring formulations for better drug release and targeting [10].

These technologies integrate computational models for personalized treatment, leveraging insights from patient-specific pharmacokinetics and imaging data. AI enhances nanocarrier design efficiency and supports rapid prototyping of smart, stimuli-responsive carriers for neurological applications while overcoming biological barriers like the blood-brain barrier [11].

Structure and Function of the BBB

The BBB is primarily formed by specialized endothelial cells that line the capillaries in the brain. These endothelial cells are connected by tight junctions, which are protein complexes that seal the gaps between cells, preventing the passage of large molecules and pathogens [12]. In addition to tight junctions, the BBB is also supported by pericytes, astrocytes, and the basement membrane, all of which play important roles in maintaining the integrity of the barrier [13]. The Blood-Brain Barrier (BBB) is a term used to describe the unique properties of the microvasculature of the Central Nervous System (CNS) [14]. CNS vessels are continuous non-fenestrated vessels but also contain a series of additional properties that allow them to tightly regulate the movement of molecules, ions, and cells between the blood and the CNS [15]. This heavily restricting barrier

capacity allows BBB ECs to tightly regulate CNS homeostasis, which is critical to allow for proper neuronal function, as well as protect the CNS from toxins, pathogens, inflammation, injury, and disease [16]. The restrictive nature of the BBB provides an obstacle to drug delivery to the CNS, and, thus, major efforts have been made to generate methods to modulate or bypass the BBB for the delivery of therapeutics [17]. Loss of some, or most, of these barrier properties during neurological diseases including stroke, Multiple Sclerosis (MS), brain traumas, and neurodegenerative disorders, is a major component of the pathology and progression of these diseases [18].

These blood vessels are made up of two main types of cells namely, endothelial cells and mural cells. These endothelial cells are mesodermally derived modified simple squamous epithelial cells that form the walls of blood vessels [19]. Microvascular ECs are extremely thin cells that are 39% less thick than muscle ECs, with a distance of less than a quarter of a micron separating the luminal from the parenchymal surface. For morphology, the endothelial cells in the BBB are fastened by both tight junctions and adherens junctions, resulting in distinct luminal and abluminal membrane compartments [20]. The functions of these ECs are, first, they display a net negative surface charge, refusing to accept negatively charged compounds, as well as quite low degrees of leukocyte adhesion molecules, hampering the entry of the number of immune cells [21]. Second, they show designated transporters for regulating the inflow and outflow of specific substrates. Third, they show a restriction on the number of transcellular vesicles through the vessel wall due to the high transendothelial electrical resistance. Because of the existence of the local environment, endothelial cells can together form and maintain the BBB. Molecules cross the BBB by a paracellular pathway (between adjacent cells) or a transcellular pathway (through the cells) [22]. For the paracellular pathway, ions, and solutes utilize concentration gradients to pass the BBB by passive diffusion. The transcellular pathway includes different mechanisms such as passive diffusion, receptor-mediated transport, and transcytosis [23]. Overall, passive diffusion is a non-saturable mechanism dependent on the physicochemical properties of the molecule. The physicochemical factors that influence BBB permeability include molecular weight, charge, lipid solubility, surface activity, and relative size of the molecule [24]. The BBB performs 3 major functions: it curbs free transport between the blood and the brain, essential nutrients are supplied to the brain through it, and it aids in the flow of any harmful or toxic waste or foreign substances [25]. The brain endothelial cells that form the BBB express transport proteins. These are mostly separated within either the luminal or abluminal surfaces, which mainly give expressions for the transport of peptides, proteins, and neurotransmitter-metabolizing enzymes [26].

CHAPTER 6

Clinical Strategies, Management, and Challenges in Targeting CNS through Bioactive Compounds

Abstract: The Central Nervous System (CNS) plays a pivotal role in regulating essential physiological processes, highlighting the critical need for effective therapeutic interventions targeting CNS disorders. Bioactive compounds, including small molecules and peptides, offer promising avenues for CNS drug discovery and development by modulating specific molecular targets implicated in neurological pathophysiology. However, the Blood-Brain Barrier (BBB) poses a formidable obstacle to CNS drug delivery, necessitating innovative approaches such as nanoparticle delivery systems, viral vectors, and alternative delivery methods like convection-enhanced delivery. This chapter comprehensively explores clinical strategies, management approaches, and challenges associated with targeting the CNS through bioactive compounds. It examines pharmacokinetic and pharmacodynamic considerations relevant to CNS drug delivery, highlighting innovative technologies and formulation approaches aimed at enhancing therapeutic efficacy. Despite significant progress, formidable challenges persist, including the complexity of CNS biology, the risk of off-target effects, and stringent regulatory requirements. Future research directions encompass developing better preclinical models, exploring multi-target approaches, and implementing early intervention strategies supported by advanced biomarkers to address the global burden of neurological disorders effectively.

Keywords: Animal models, Bioactive compound, CNS, Management, Personalized medicine.

INTRODUCTION

The Central Nervous System (CNS) serves as the command center of the human body, comprising the brain and spinal cord, and orchestrating a myriad of physiological processes essential for life. The intricate network of neurons and neurotransmitters within the CNS regulates sensory perception, motor function, cognition, and emotion, underscoring its indispensable role in human health and well-being. Consequently, dysfunction or pathology within the CNS can manifest as a diverse array of neurological disorders, ranging from neurodegenerative diseases like Alzheimer's and Parkinson's to psychiatric conditions such as depression and schizophrenia [1]. Given the profound impact of CNS disorders on

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individuals and society at large, there exists a pressing need for effective therapeutic interventions that can target the underlying mechanisms of these conditions. Bioactive compounds, including small molecules, peptides, and biologics, represent a promising avenue for CNS drug discovery and development due to their ability to modulate specific molecular targets implicated in neurological pathophysiology [2]. The scope of this chapter encompasses a comprehensive exploration of the clinical strategies, management approaches, and challenges associated with targeting the CNS through bioactive compounds. By elucidating the complex interplay between drug molecules and the CNS environment, this chapter aims to provide a nuanced understanding of the opportunities and obstacles inherent in this endeavor. In subsequent sections, we will examine in detail the pharmacokinetic and pharmacodynamic considerations relevant to CNS drug delivery, with a particular focus on overcoming the Blood-Brain Barrier (BBB) a formidable obstacle that limits the entry of therapeutics into the brain parenchyma [3]. The case studies presented in the discussion illustrate the treatment outcomes for various CNS illnesses, with several studies indicating enduring improvements over time. Patients with Parkinson's Disease (PD) who participated in exercise regimens, for instance, had sustained gains in strength, gait, and range of motion. The administration of Riluzole to patients with Amyotrophic Lateral Sclerosis (ALS) also resulted in stable functional scores over time, suggesting a good response even though the disease is progressing. Myasthenia gravis follow-up data showed improved quality-of-life ratings and successful self-management after discharge. Following intense physiotherapy sessions, long-term results from therapies such as intravenous immunoglobulin therapy for Acute Motor Axonal Neuropathy (AMAN) indicate notable improvements in strength, balance, and mobility [4].

Innovative treatments, while promising, can sometimes result in difficulties or negative effects. For example, because of the possibility of neurotoxicity, patients receiving large doses of methotrexate for Primary Central Nervous System Lymphoma (PCNSL) need to be closely monitored. Even while dopaminergic treatments for Parkinson's disease are successful, they can occasionally cause motor problems that need further control techniques. Risks associated with intrathecal therapy, such as those for spinal muscular atrophy, include unfavorable immunological reactions and local inflammation. In order to minimize potential consequences, these cases highlight the significance of individualized approaches, close observation, and prompt intervention [5].

The emerging trend of combination therapies aimed at synergistically targeting multiple disease pathways. Through a series of case studies and clinical vignettes, we will illustrate the practical application of these principles in real-world patient care scenarios. Despite the considerable progress made in CNS drug discovery

and development, significant challenges persist, posing formidable barriers to therapeutic success. These challenges include the inherent complexity of CNS biology, the risk of off-target effects and toxicity, poor patient compliance and adherence to treatment regimens, and the stringent regulatory requirements governing CNS drug approval [6].

Neurological Disorders and Therapeutic Targets

Neurological disorders impose a significant burden on global health, accounting for 3% of the worldwide disease burden. Key neurological disorders include Alzheimer's, Parkinson's disease, multiple sclerosis, epilepsy, and headache disorders (migraine, tension-type headache, and medication-overuse headache). Despite representing a seemingly small overall percentage, conditions like dementia, epilepsy, migraine, and stroke rank among the top 50 causes of disability-adjusted life years (DALYs). Migraine and epilepsy are particularly impactful, comprising one-third and one-fourth of the neurological burden, respectively. Dementia and Parkinson's disease have shown a substantial increase in burden over the past decade [7].

Neurological disorders, such as epilepsy, dementia, and headache disorders, present significant global health challenges, accounting for 3% of the worldwide disease burden. Epilepsy, characterized by recurrent unprovoked seizures, has higher prevalence and incidence rates in low- and middle-income countries (LMICs) due to factors like endemic conditions (*e.g.*, malaria), injuries, and inadequate healthcare infrastructure [8]. The median incidence in LMICs is 81.7 per 100,000 annually compared to 45.0 in high-income countries (HICs). Premature mortality from epilepsy is the highest in LMICs, driven by preventable causes such as status epilepticus and accidents. Globally, epilepsy is the 36th leading cause of disability-adjusted life years (DALYs) and the 20th leading cause of years lived with disability (YLDs), second to migraine among brain disorders [9].

Dementia, affecting cognitive functions and daily activities, poses a growing burden, particularly in aging populations. Approximately 47 million people had dementia in 2015, with projections indicating this will nearly triple by 2050, predominantly in LMICs. Despite its increasing prevalence, dementia is often stigmatized and misunderstood, leading to delayed diagnoses and inadequate care [10]. This gap is exacerbated by the scarcity of pharmacological and psychosocial interventions in LMICs. Dementia includes Alzheimer's disease, vascular dementia, and other forms, with Alzheimer's accounting for 50-60% of late-life cases. The incidence of dementia doubles every five years after age 65, highlighting the impact of aging populations on the global burden [11].

CHAPTER 7

Intellectual Properties and Current Treatment Strategies for Targeting Neurodegenerative Disorders

Abstract: Neurodegenerative disorders, including Alzheimer's, Parkinson's, Huntington's, and Amyotrophic Lateral Sclerosis (ALS), pose significant challenges due to their progressive nature and debilitating effects on patients' quality of life. Recent advancements in biomedical research have spurred the development of novel therapeutic strategies aimed at modifying disease progression and improving patient outcomes. These strategies encompass a wide array of approaches such as small molecule drugs, biologics, brain and physical exercises, gene therapy, AI-based diagnosis and treatment, nano-bioactive approaches, and innovative drug delivery systems designed to enhance Central Nervous System (CNS) penetration and target specific pathological mechanisms. Despite these promising developments, the complexity of neurodegenerative diseases necessitates multifaceted treatment paradigms that combine neuroprotection, neuronal restoration, and symptomatic management. However, several challenges persist. The Blood-Brain Barrier (BBB) remains a significant obstacle to effective drug delivery, while the heterogeneous nature of these diseases requires personalized treatment approaches. Also, safety and management of the side effects of advanced therapies such as gene therapy and brain stimulation techniques are critical concerns. The Intellectual Property (IP) landscape further complicates the development of new treatments. Navigating this complex terrain involves dealing with overlapping patents, the expiration of early patents leading to increased competition, and the high costs associated with bringing new therapies to market. Ethical and legal considerations, particularly concerning advanced technologies, add another layer of complexity.

Keywords: Blood-brain barrier, Intellectual property, Neurodegenerative disorders, Nano-bioactive approaches, Neuroprotection.

INTRODUCTION

Neurological disorders are characterized by the progressive degeneration of the structure and function of the nervous system, leading to debilitating symptoms and a profound impact on a patient’s quality of life. Despite extensive research, effective treatments remain limited, primarily offering symptomatic relief rather

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than addressing the underlying causes of neurodegeneration [1]. Some recent advancements in biomedical research have spurred the development of novel therapeutic strategies aimed at modifying the treatment of disease by progression and improving patient outcomes. These strategies include a wide array of approaches such as small molecule drugs, biologics, brain exercise and physical exercise, gene therapy, AI-based diagnosis and treatment approach, nano-bioactive approach, and innovative drug delivery systems designed to enhance Central Nervous System (CNS) penetration and target specific pathological mechanisms [2, 3]. The complexity of neurodegenerative diseases necessitates multifaceted treatment paradigms that combine neuroprotection, neuronal restoration, and symptomatic management. Patents play a critical role in fostering innovation by providing exclusive rights that encourage investment in research and development. Navigating the IP landscape presents unique challenges due to the intricacies of neurodegenerative mechanisms and the need for precise and effective targeting within the CNS [4].

Various Approaches for the Treatment of NDDs

Timely identification of neurodegenerative disorders is critical to the efficacy of a given therapy in slowing down their course. Treatment can be started before the onset of severe clinical symptoms and can be considerably delayed by early detection through screening [5].

Neurodegenerative disorders are characterized by a complicated scenario of dying tissue involving various cell types and mediators, often with uncertain etiology. Regardless of where they originate, oxidative stress, neuroinflammation, and cell death are the fundamental mechanisms shared by all neurodegenerative diseases of the Central Nervous System (CNS). When compared to other therapeutic fields, the range of therapy options for neurological disease is restricted, and the medication approval rates for improved treatments continue to be low. The treatment of neurodegenerative diseases aims to slow down the degeneration's pace and enhance patients' quality of life because the degradation of neural tissue is irreversible. Pharmacotherapy alters the metabolism of neurons and glial cells to slow down degenerative processes [6].

Pharmacological Approach

One of the most difficult problems facing modern biomedicine is the development of effective therapeutic techniques for treating neurological disorders. The lack of medications that alter the pathophysiology of the disease is the main problem. Thus yet, no fundamental treatment that could provide substantial advantages to individuals suffering from harmful conditions has been created. Numerous *in vitro* and *in vivo* models are available for the research of neurodegenerative disorders,

such as animal models of disease and cell models using induced pluripotent stem cells and brain organoids. Recent research has focused on microtubule stabilizing agents—natural or synthetic—that can stop tau protein disorders from destroying axons. Current therapeutic approaches can only momentarily alleviate a patient's symptoms, which include cognitive deficits and impaired motor function. On the other hand, average life expectancy has significantly grown along with the number of age-related disorders due to advances in our quality of life. Therefore, in contemporary medicinal chemistry, finding new targets for therapeutic action, creating novel synthesis techniques, and selecting possible neuroprotectors based on their targets are all crucial [7].

Since targeting transcriptional regulators would cause a broad alteration in numerous impacted downstream processes, this strategy may prove advantageous in the fight against neurodegenerative diseases [8]. This feature, however, also raises the possibility of a warning since not all genes that are involved in the pathogenesis may be negatively impacted by changes to their transcription. Abnormal protein aggregation is caused by errors in the breakdown of misfolded proteins, which is a characteristic of several neurodegenerative disorders. The inadequate elimination of pathogenic proteins, including tau, Aβ, and α-synuclein, can be ascribed to an autophagic breakdown [9].

Gene-based therapy

A potential area of research is the application of gene therapy to treat neurodegenerative disorders. This involves altering a patient's genes to halt the progression of certain diseases, such as those affecting the nervous system. There is a resurgence in gene therapy. Gene-based therapies, which encompass all types of genome alteration, hold great appeal for treating neurodegenerative disorders, for which traditional pharmaceutical techniques have shown to be mostly ineffective [10]. These therapies offer the dual promise of addressing the etiology of the disease and providing “long-term correction.” A paradigm for such therapeutic intervention and a foundation are provided by the recent success of viral-vector-based gene therapy in spinal muscular atrophy, which improved survival and motor function with a single intravenous injection [11]. While there are still obstacles to overcome, the renewed hope is primarily due to advancements in the development of viral vectors that can disperse genes throughout the central nervous system and genome-engineering instruments that may modify disease pathways in previously unfeasible ways. It is impossible that spinal muscular atrophy is the only neurodegenerative condition [12].

The process of changing a person's genes to treat or prevent a disorder is known as gene therapy. Several methods are used to do this, including swapping out the

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Rishabha Malviya

Rishabha Malviya did Ph.D. pharmacy in the area of novel formulation development techniques. He has 12 years of research experience and presently working as associate professor in the Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University for the past 8 years. His area of interest includes formulation optimization, nanoformulation, targeted drug delivery, localized drug delivery and characterization of natural polymers as pharmaceutical excipients. He has authored more than 150 research/review papers for national/international journals of repute. He has 51 patents (12 grants, 38 published, 1 filed) and publications in reputed national and international journals. He received an outstanding reviewer award from Elsevier. He has authored/edited 21 books and 15 book chapters. He is reviewer/editor/editorial board member of more than 50 national and international journals of repute.

Sudhanshu Mishra

Sudhanshu Mishra completed M. Pharm in pharmaceutics from the School of Pharmaceutical Science, Rajiv Gandhi Proudyogiki Vishwavidyalaya, Bhopal, and is pursuing Ph.D. from Dr APJ Abdul Kalam Technical University, Lucknow, Uttar Pradesh. He is currently working as an assistant professor at the Faculty of Pharmaceutical Sciences, Mahayogi Gorakhnath University Gorakhpur. His areas of interest include novel formulations, nano-herbal formulation, transdermal drug delivery, localized drug delivery, etc. He has authored over 50 research/review articles for national/international journals. He is a reviewer and editorial board member of national and international journals. He also has participated in different academic activities like international seminars, conferences, workshops, and oral presentations.

Shivendra Mani Tripathi

Shivendra Mani Tripathi is currently working as an assistant professor at the Faculty of Pharmaceutical Sciences, Mahayogi Gorakhnath University Gorakhpur. He is currently pursuing Ph.D. from Banasthali Vidyapeeth. He completed a Masters in pharmacy with a specialization in pharmacology from Amity University, Lucknow, Uttar Pradesh, India. He has one year of teaching experience and has experience with drug designing software, such as AutoDock 4.2.6, MGL Tools, Open Babel, Discovery Studio, and Chem Sketch. He is also familiar with databases, such as PubChem and Drug Bank, and has proficiency in using MS Excel, MS Word, MS PowerPoint, and Graph Pad Prism 5.0.

Smriti Ojha

Smriti Ojha graduated in Pharmacy from Dr. B. R. Ambedkar Agra University, Agra and post graduate from Uttar Pradesh Technical University, Lucknow in Pharmaceutics. She earned a doctorate in pharmaceutical sciences from Dr. A. P. J. Abdul Kalam Technical University, Lucknow. Her doctoral research focused on development of solid lipid nanoparticles for better management of multiple sclerosis. She has a teaching and research experience of around 18 years and is currently working as associate professor in the Department of Pharmaceutical Science and Technology, Madan Mohan Malaviya University of Technology, Gorakhpur, Uttar Pradesh. She is actively engaged in the research area of oral and controlled drug delivery, and nanotechnology. She has published more than 50 peer-reviewed research papers in prestigious national and international journals. She has authored three books and a number of papers that serve as valuable resources for students and professionals in the field of pharmaceutics. She has also contributed to more than fifteen book chapters. Her expertise is in novel drug delivery systems and nanotechnology.