UNRAVELLING ALZHEIMER'S

INNOVATIONS IN PATHOGENESIS, DIAGNOSIS, AND THERAPEUTICS

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Unravelling Alzheimer's: Innovations in Pathogenesis, Diagnosis, and Therapeutics

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FOREWORD

Unravelling Alzheimer's: Innovations in Pathogenesis, Diagnosis, and Therapeutics

Alzheimer's disease stands as one of the most formidable challenges to global health in the 21st century. As populations age and life expectancy increases, the burden of neurodegenerative diseases, particularly Alzheimer's, has grown exponentially, touching countless lives and posing significant emotional, social, and economic tolls. The urgency to understand, diagnose, and treat this devastating disorder has never been more critical.

It is against this backdrop that Unravelling Alzheimer's: Innovations in Pathogenesis, Diagnosis, and Therapeutics emerges as a timely and impactful scholarly contribution. Edited by Mr. Sudhanshu Mishra and Dr. Raghav Mishra, along with a dedicated team of experts, this volume brings together a diverse and interdisciplinary exploration of the many facets of Alzheimer's disease from its complex pathogenesis to state-of-the-art diagnostic approaches, and from natural therapeutics to gene and immunotherapy innovations.

The book thoughtfully integrates traditional knowledge and cutting-edge science. It explores the potential of natural compounds and phytochemicals while simultaneously embracing the future of diagnostics through artificial intelligence, neuroimaging, and biomarker discovery. The inclusion of gene therapy, RNA-based solutions, and emerging pharmacological treatments reflects the depth and foresight of the contributors. Equally valuable are the discussions surrounding comorbidities, intranasal drug delivery systems, and real-world insights gleaned from patents and case studies.

I commend the editors and contributors for their vision, dedication, and scholarly excellence in assembling this important body of work. This book is not just a repository of knowledge; it is a call to action for deeper inquiry, innovation, and hope in the fight against Alzheimer's disease.

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PREFACE

Alzheimer's Disease (AD), a progressive neurodegenerative disorder, represents one of the most formidable challenges in contemporary medicine and neuroscience. As global populations age, the incidence of Alzheimer's continues to rise, exerting profound social, economic, and healthcare burdens across the world. This book, Unravelling Alzheimer's: Innovations in Pathogenesis, Diagnosis, and Therapeutics, provides a comprehensive and multidisciplinary overview of the latest advancements in our understanding, diagnosis, and treatment of Alzheimer's disease. The book begins by exploring the historical background, epidemiology, and global impact of Alzheimer's Disease, laying the foundation for a deeper understanding of its pathophysiology. A thorough examination of the molecular and cellular mechanisms underpinning Alzheimer's progression is presented, followed by insights into biomarkers and their emerging role in early detection and therapeutic targeting.

Technological progress has redefined diagnostic approaches, and the book highlights the growing utility of neuroimaging techniques and digital tools, including artificial intelligence, in enhancing diagnostic precision. In addition, a significant portion is dedicated to natural products, phytochemicals, immunotherapies, gene therapy, and RNA-based innovations, showcasing novel therapeutic frontiers. Recognizing the multifactorial nature of Alzheimer's, chapters also delve into comorbid conditions that influence disease progression, as well as the latest developments in pharmacological treatments and intranasal drug delivery strategies. The inclusion of case studies and patents further connects theoretical advancements with real-world applications, offering a well-rounded perspective on ongoing innovation in the field.

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This volume brings together contributions from experts across diverse disciplines, making it a valuable resource for clinicians, researchers, students, and pharmaceutical professionals. It aims not only to consolidate current knowledge but also to inspire future research directions and therapeutic breakthroughs.

We trust that this book will serve as a valuable guide in your exploration of Alzheimer's disease and stimulate continued inquiry into innovative solutions for this pressing global health issue.

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CHAPTER 1

Introduction to Alzheimer's Disease: History, Epidemiology, and Global Impact

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Abstract: Alzheimer's Disease (AD) is a progressive neurodegenerative condition and the leading cause of dementia, marked by memory impairment, cognitive deterioration, and alterations in behaviour. Initially identified by Alois Alzheimer in 1906, the disorder has since garnered significant attention within the field of neuroscience. The defining pathological characteristics include the presence of extracellular amyloid-beta plaques, intracellular neurofibrillary tangles formed by hyperphosphorylated tau protein, and extensive neuronal degeneration. On a global scale, AD poses a considerable public health issue, currently affecting over 55 million individuals with dementia, a figure anticipated to rise beyond 139 million by 2050 due to the aging population. The disease predominantly impacts those aged 65 and older, with a higher incidence observed in women. Contributing factors to the development of AD encompass genetic vulnerabilities, such as mutations in the allele, alongside modifiable elements like cardiovascular health, educational attainment, and lifestyle choices. The economic and social ramifications of AD are significant, with an estimated annual global expenditure exceeding $1 trillion, which includes healthcare costs, caregiving expenses, and lost productivity. Furthermore, the emotional toll on families and caregivers is considerable, often resulting in psychological distress and financial hardship. Epidemiological research indicates variations in the prevalence and incidence of AD across different regions, shaped by demographic, cultural, and healthcare-related factors. Initiatives to combat AD include progress in early diagnostic methods utilizing biomarkers and neuroimaging, the creation of disease-modifying treatments, and public health strategies focused on prevention through the management of risk factors. This review seeks to present a comprehensive overview of the historical context, epidemiology, and global implications of AD, highlighting the pressing necessity for ongoing research and international cooperation to address this escalating crisis.

Keywords: Alzheimer's disease, Dementia, Epidemiology, Neuronal degeneration, Neuroscience.

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Prashant Kumar Dhakad, Raghav Mishra, Shweta Sharma, Sudhanshu Mishra & Nishant Gaur (Eds.)

INTRODUCTION

History of Alzheimer's Disease

Alzheimer's disease (AD) is a relentless, advanced neurodegenerative condition that affects widespread regions of the cerebral cortex and hippocampus. Initial deviations are typically observed in the brain tissue of the temporal as well as frontal lobes, gradually spreading to other zones of the neocortex at varying rates among individuals. This disease is defined by the accumulation of insoluble amyloid-β in plaques within extracellular spaces and blood vessel walls, along with the clustering of the microtubule protein tau into neurofibrillary tangles inside neurons. Amyloid-β originates from the proteolytic cleavage of amyloid precursor protein by a complex array of enzymes, including γ-secretases and β-secretases, which involve presenilin 1 and presenilin 2 [1]. Several stages of AD with their symptoms are stated in Table **1**.

Table 1. Phases of Alzheimer's disease with their symptoms/characteristics.

STAGE	SYMPTOMS/CHARACTERISTICS	REFERENCES
Preclinical AD	Categorized by identifiable biomarkers and observable alterations in the brain, blood, and cerebrospinal fluid, despite the nonappearance of symptoms like impairment of memory.	[5, 6]
Cognitive Impairment [Mild]	Mild Cognitive Impairment due to AD presents assessable biomarkers and brain variations associated with AD pathology, alongside a moderate decline in cognitive function. This decline is primarily evident in the implementation of daily routine activities, like managing bills or preparing meals, which require more time and exhibit reduced efficiency.	[7, 8]
Dementia	It is marked by measurable biomarkers and brain changes linked to the pathology of AD, alterations in behaviour, and severe difficulties in performing daily responsibilities.	[9]

The average lifespan of the illness ranges from 8-10 years, but the characteristic phases are headed by preclinical stages that can last up to two decades. The most prevalent form is sporadic AD, with a typical onset around the age of 80. The primary issue lies in the brain's inability to eliminate the amyloid-β peptide. Additionally, co-existing conditions such as cerebrovascular disease and sclerosis are common at this age, complicating both diagnosis and treatment. While it is not uncommon for individuals with sporadic Alzheimer's to have a family history of the disease, a small fraction (<1%) of patients experience autosomal dominant inherited Alzheimer's disease, which typically manifests much earlier, around the age of 45. In this group, PS1 and PS2 lead to either excessive production or the creation of an abnormal form of amyloid-β. In many clinical aspects, sporadic and familial AD are similar, including the pace of disease evolution and biomarker

characteristics. AD, as a distinct medical condition, exhibits numerous similarities with other neurodegenerative disorders that are defined at the molecular level, including Parkinson's disease and frontotemporal dementias [2]. The stages of Alzheimer's disease, with their severity range, occur in the form of amyloid plaque and neurofibrillary tangles, are shown in Fig. (**1**).

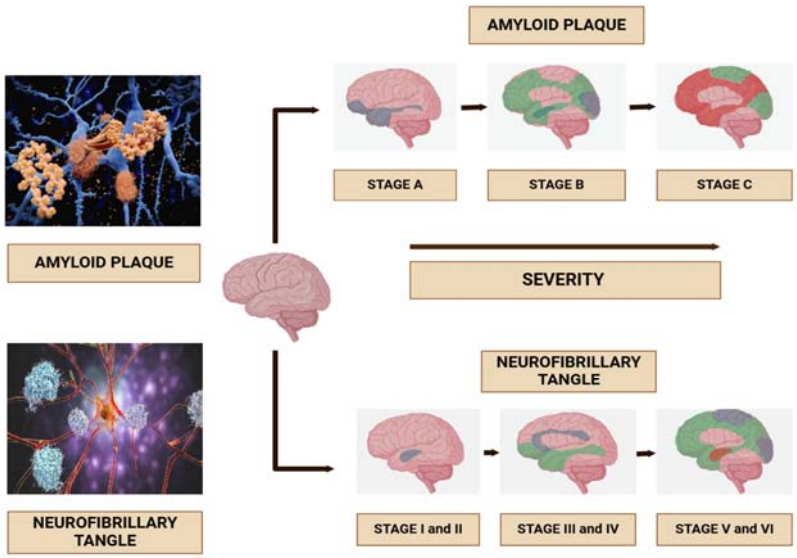

Fig. (1). Stages of Alzheimer's disease.

AD—recognized as the utmost prevalent kind of dementia—was first described in 1906 by the German psychiatrist Alois Alzheimer. He presented the case of Auguste Deter, a 51-year-old woman suffering from significant memory impairment and cognitive deterioration. After her death, Alzheimer examined her brain and identified amyloid plaques and neurofibrillary tangles, now recognized as key markers of the disease [3].

Initially considered rare and affecting younger individuals, Alzheimer's was later found to be a leading cause of dementia in older adults as life expectancy increased. The mid-20th century saw major progressions in neuropathology and biochemistry, including the discovery of amyloid-beta in 1984 and tau protein in 1985, both crucial to the disease's development. Further research in the late 20th and early 21st centuries uncovered genetic factors, such as APP, PSEN1, PSEN2, and the APOE ε4 allele, highlighting its hereditary aspects. Developments in neuroimaging and biomarkers have improved early diagnosis and disease monitoring. Despite these discoveries, Alzheimer's remains a major global health

CHAPTER 2

Pathophysiology and Molecular Mechanisms of Alzheimer's Disease

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Abstract: Alzheimer's Disease (AD), the leading cause of dementia worldwide, remains without an effective cure, largely due to an incomplete understanding of its underlying mechanisms. Recent research highlights the central roles of amyloid β (Aβ) and tau proteins, alongside glial cell dysfunction, in the pathogenesis of AD. This chapter reviews advances in Aβ- and tau-related mechanisms, focusing on neuronal and glial receptors mediating Aβ toxicity and the role of glial cells in neurodegeneration. Early neurodegeneration in AD is marked by neuronal loss and synaptic impairment. Despite significant progress in uncovering AD's molecular mechanisms, the disease's complex pathogenesis and limited diagnostic and therapeutic tools have hindered the development of effective treatments. Comprehensive disease modelling is imperative to clarify AD's mechanisms and facilitate the creation of targeted therapies. Mitochondrial dysfunction, oxidative stress, and chronic neuroinflammation emerge as critical mediators of neuronal damage, emphasizing the multifactorial nature of AD. This chapter reviews the interplay between inherited risk, aging, lifestyle factors, and environmental exposures in influencing AD pathogenesis. Additionally, it will explore how these factors contribute to the broader molecular and cellular pathways involved in disease progression. Microglial activation and astrocytic dysfunction significantly influence the progression of neuronal injury and synaptic loss, underscoring their importance in AD pathogenesis. Emerging evidence underscores the importance of understanding glial contributions to neuronal dysfunction, offering new perspectives on disease progression and potential intervention points. The transition from early-stage molecular alterations to widespread neuronal dysfunction and clinical decline underscores the importance of early pathophysiological insights. Recent advancements in understanding AD's complex pathophysiology provide promising avenues for enhanced diagnostics, assessing risks more accurately, and novel prevention strategies. These discoveries bring hope for improved management and therapeutic options for the millions affected by this debilitating condition.

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Keywords: Alzheimer's disease, AD, Molecular mechanisms, Pathophysiology alzheimer's.

INTRODUCTION

Disease Prevalence rate in India and other countries

Alzheimer's Disease (AD) is a disorder of the brain. It accounts for about 75% of all dementia cases and is the most prevalent type. Associated dementia is amongst the chief causes of debilitation in the elderly (>65 years of age); however, early onset forms of AD are also known, and these comprise ~2-5% of all Alzheimer's disease cases. It is progressive and goes undetected in its prodromal phases since there are no obvious symptoms. However, as the disease worsens and symptoms start to show, the level of neuronal damage becomes irreversible. Neuronal cells necessary for performing even basic body functions, like walking and swallowing, eventually deteriorate, leaving the patient immobile.

AD is a complicated illness that is caused by several pathogenic factors. Researchers have thus far been unable to arrive at a definite conclusion regarding what initiates the chain of events that culminates in the atrophy of the brain. The accumulation of Amyloid beta (Aβ) peptide and tau protein into highly stable aggregates termed beta-amyloid plaques and tau tangles has long been held as the central feature of this disease pathogenesis, but has been challenged in recent times. Aggregated Aβ and Tau get deposited in the neurons of the brain, extracellularly (in case of Aβ) and intracellularly (in case of tau). This is suggested to contribute to cellular and inflammatory stress, from which cells are unable to recover, and consequently, they die. Furthermore, the brain's ability to metabolize glucose also gets impaired in this disease. The disease remains incurable as of now and is a cause of anguish for millions around the globe. The multifactorial nature of this disease is the reason behind failure in contriving equate therapeutic and diagnostic measures against it. It forms a major burden to the worldwide healthcare system, and it is estimated that in the coming decade, the AD burden will vastly impact developing countries like India, which are currently lacking adequate awareness and infrastructural support to combat the rising disease cases of AD.

Alzheimer's Disease is the leading cause of dementia

In 1906, after reporting a case of dementia, Dr. Alois Alzheimer believed it to be a novel form of illness. Dr. Emil Kraepelin later gave it the name Alzheimer's disease. After a century, this disease has emerged as the most prevalent form of dementia that afflicts the elderly and poses a significant health burden. Nevertheless, there are currently no disease-modifying treatments that stop,

prevent, or even delay the disease's progression, and the pathophysiology of the condition is still unknown.

Dr. Alzheimer initially noticed that the brain of the first patient with both intracellular neurofibrillary tangles and extracellular plaques, as were seen in AD. Senile plaques, the sole distinct clinical hallmark of AD, were named after the fibrous β-amyloid peptide (Ab) that was shown to be the plaques' constituent

Probable Causes of Alzheimer's Disease

A three-part process for AD induction is put forth:

1. Increased blood ceramide.
2. Decreased blood folic acid.
3. Decreased blood lactic acid

Age-related alterations in these systems are caused by decreasing muscle mass, increased visceral fat, and nutritional changes. This procedure also explains why many people do not develop AD. It is brought on by an AD case of events that damage neurons and the blood-brain barrier. The blood–brain barrier keeps dangerous chemicals out of the brain while allowing necessary molecules to remain inside. Lactic acid, which is produced during exercise, is a brain nutrient. Endothelial cells and pericytes are harmed by lactic acid AD, which is comparable to brain damage and blood-brain barrier impairment. The blood–brain barrier is harmed in AD by adequate folate consumption and oxidative stress brought on by endothelial nitric oxide synthase and transient receptor potential cation channel activation. The final processes that lead to AD neuronal death could be modifications in microRNA levels. IL-1β, Lactic acid, ceramide, folate, Tumor necrosis factor α, kynurenine metabolites, nicotinamide, and microRNA are all implicated in a novel mode of Alzheimer's disease induction.

CORE PATHOLOGICAL FEATURES

Amyloid-beta (Aβ) plaques and their role

AD is characterized by the aberrant deposition of amyloid-beta (Aβ) protein in the brain, a process tightly linked to neuronal injury and cognitive decline [1]. Aβ, initially identified in cerebrovascular amyloid deposits, later emerged as the primary element of amyloid plaques in AD and Down syndrome [2, 3]. Aβ is generated through the enzymatic cleavage of APP via two pathways: the amyloidogenic pathway, which leads to Aβ plaques, and the non-amyloidogenic pathway, which does not [4]. In the amyloidogenic pathway, β-secretase (BACE1)

CHAPTER 3

Role of Biomarker in Treating Alzheimer's Disease

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Abstract: Alzheimer's Disease (AD) is a multifactorial neurodegenerative disease associated with progressive decline in cognitive functions. Recent advances have been made in diagnostic techniques for AD by using Biomarkers. Biomarkers are not mere indicators of their pathophysiology but are the key to optimizing and making clinical decisions and therapeutic strategies. Biomarkers have thus become crucial elements in the diagnosis, monitoring, and treatment of AD. Early detection of AD is also essential for interventions, and biomarkers in AD, such as the development of senile plaques through aggregation of amyloid-beta and neurofibrillary tangle formation through tau proteins, and in recent years, new trends have been made towards the detection of Ocular biomarkers are considered important contributors in the diagnosis of AD. Ocular biomarker is an important biomarker because the nervous system of the eyes is considered an extension of the CNS. So, biomarkers help in distinguishing the cause of dementia in cognitive disorders like AD and thereby provide a target for therapeutic strategies. As the disease progresses, levels of biomarkers can be monitored for clinical manifestation, thus informing healthcare providers about disease trajectories in patients and changing the therapeutic approach correspondingly. "For instance, *via* examination of the cerebrospinal fluid, neuroimaging, or related techniques, valuable information on the pathology of AD may be obtained, which helps in tracking neurocognitive decline. Biomarkers also play a critical role in the assessment of treatment efficacy". Objective measures, reduction in amyloid burden as measured by PET scans, can be an indication of good response to amyloid-targeting therapies and direct further treatment. Further studies on new biomarkers, including neuroinflammatory markers and genetic variants, will provide further refinement of personalized treatment approaches, thereby helping improve the outcomes of the patients. To enhance the appropriate early diagnosis and proper monitoring plus targeted treatment interventions, these biomarkers should be integrated into the clinical care of AD. It is now clear from other various studies that this might change the way AD is treated and improve the standard of care.

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Keywords: Alzheimer's disease, Amyloid-beta, Biomarkers, CNS, CSF, Dementia, Genetic variants, Neuroimaging, Ocular Biomarkers, Tau proteins.

INTRODUCTION

Alzheimer's Disease (AD) remains a public health challenge, with a current prevalence of 10% in the 65 to 74-year-old population and up to 40% post age 85. At the molecular level, AD is characterized by extracellular aggregation of beta-amyloid plaques; intracellular aggregation of hyperphosphorylated tau protein, resulting in the formation of neurofibrillary tangles; synaptic dysfunction; and neurodegeneration, which impairs cognitive function. It has been more than a century since Alzheimer's disease was discovered, and we have a sophisticated understanding of disease pathology and progression. However, due to the lack of a complete understanding of the etiology, development, and toxic pathways, the clinical toolkit for diagnosing and treating patients with AD today is still very limited [1, 2]. Currently, there is no cure for this disease. Disease-modifying treatments could theoretically be established before the onset of symptoms or at an early stage, but this may necessitate the use of risk-linked biomarkers for therapeutic trials and interventions. The discovery of these risk-linked biomarkers is in part due to a deeper understanding of the disease and the subsequent identification and development of potential AD therapies [3, 4].

The discovery of biomarkers of pathophysiological alterations, often referred to as 'amyloid toxicity' or 'neurodegeneration', has modified the pathological framework of AD, which was initially based on the clinical, imaging, and neuropathological evidence of Aβ deposition and NFT buildup in animal models and individuals. These insights allow a much earlier and more accurate detection and risk estimation of AD dementia—the main clinical target being tests for Aβ and tau under an increasing global challenge resulting from the growing underestimation and underdiagnosis of the disease [5]. This review describes the roles and the required characteristics of risk-linked and diagnostic AD biomarkers in relation to the different predefined stages of the disease, detailing several alternative methods through which these biomarkers can be detected in various biological matrices; it refers to the complementary use that these biomarkers should have for correctly diagnosing an individual in routine clinical practice and during and after clinical trials, and presents an algorithm based on a new staging system of AD that underlines three preclinical and three dementia-specific stages in these cases [6, 7].

A Brief on Alzheimer's Disease

Alzheimer's Disease (AD), which affects up to two-thirds of dementia cases, is characterized by the appearance of two classes of brain lesions in histopathological examination, namely senile plaques and neurofibrillary tangles. Plaques are primarily compounds of insoluble beta-amyloid, whereas the neurofibrillary tangles are composed of an abnormal form of a microtubule-associated protein. The current breakthrough descriptions of AD pathophysiology have centered on changes secondary to the sarcoplasmic-endoplasmic reticulum [8]. The most important of these descriptions is secondary impairment of intraneuronal calcium homeostasis; this has served as the foundation of a firm biochemical AD model. The development makes possible advances beyond post-mortem secular AD practice and understanding pre-mortem AD biology. In combination with other data suggesting a critical role of the endoplasmic reticulum, calcium biology, tau biology, inflammation, oxidation, or glucose and lipid utilization in the predisposition to cognitive disorders, the development forms the pillars of a credible hypothesis regarding the early pathogenesis of cognitive disorders [9, 10].

Current attempts to treat AD are controversial. They rely on a "monolithic" model where dementia is the endpoint of pathology and all individuals may benefit from slowing the progression of pathology regardless of etiology. Finally, the "monolithic" model does not require population risk stratification. While this is a convenient public health model, it contradicts our concepts of geriatric medicine and personalized AD treatment. The recent description of sarcoplasmic-endoplasmic reticulum calcium homeostasis impairment as a signature of AD biology and as an early event associated with the biological pathogenesis of cognitive disorders may represent a substantial advance in cognitive disorder care. In combination with other data suggesting critical roles for the endoplasmic reticulum, tau biology, inflammation, glucose, and lipid metabolism in the predisposition to cognitive disorders, the endoplasmic reticulum hypothesis may serve as a major regulatory tool, guiding the development of pertinent biomarkers toward early identification of preclinical AD biology and targeted early AD treatment [11, 12].

Biomarkers as an Efficient Tool in AD Management

Introduction and Aim: Accurate and efficient tools for diagnosing and treating Alzheimer's disease (AD) are essential for controlling the economic and medical burden of AD and for extending a patient's quality of life. The review article aims to create an in-depth and comprehensive resource for clinicians, researchers, and policymakers to understand the role of cerebrospinal fluid (CSF), plasma, and

CHAPTER 4

Neuroimaging and Advanced Techniques in Alzheimer's Diagnosis

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Abstract: Globally, dementia is a major cause of death and disability. The early, precise, and differential diagnosis of dementia and Alzheimer's disease depends on neuroimaging or brain imaging. Because of structural and molecular imaging, which is also increasingly being employed in clinical practice for early and accurate diagnosis, the pathogenesis of neurodegenerative dementias has been better understood. Several neuroimaging techniques that are regarded as state-of-the-art diagnostic aids were highlighted. Most of the research that uses imaging modalities for early diagnosis is preventive studies. The accurate identification of AD biomarkers is made possible by AI-enhanced neuroimaging methods such as MRI, PET, and CT scans. With technologies that improve the precision of neuropsychological testing and examine speech and language patterns for early indicators of dementia, artificial intelligence has also enhanced cognitive and behavioural examinations. The MRI modalities discussed encompass structural MRI, functional MRI, diffusion tensor imaging, magnetic resonance spectroscopy, and arterial spin labelling. These advanced techniques enable the identification of presymptomatic diagnostic biomarkers in the brains of cognitively normal older adults and can also be utilized to track Alzheimer's disease progression following the emergence of clinical symptoms. Advanced MRI techniques, such as arterial spin labelling and Diffusion Tensor Imaging (DTI), are also being explored to better understand Alzheimer's disease. In PET imaging, ongoing efforts focus on developing high selectivity and affinity ligands. As no single imaging method is adequate for early diagnosis, this has led to the emergence of a new approach known as "multi-modal imaging."

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Keywords: AI-enhanced diagnosis, Diffusion tensor imaging, Magnetic resonance imaging, MRI modalities, Neuroimaging.

INTRODUCTION

The most common type of dementia, Alzheimer's Disease (AD), is defined by a progressive loss of cognitive abilities that limits a person's ability to carry out daily tasks by impacting memory, thinking, and social skills. The pathological basis of Alzheimer's Disease (AD) is the accumulation of neurofibrillary tangles and amyloid plaques, primarily composed of hyperphosphorylated tau proteins and amyloid-beta (Aβ) peptides, respectively. These pathological processes drive neurodegeneration and synaptic loss, ultimately leading to profound cognitive and behavioral impairments [1, 2].

As the global population ages, the prevalence of AD is expected to increase markedly. Current estimates suggest that approximately 47 million individuals are affected worldwide, with a new case diagnosed every 35 seconds. This demographic trend highlights the urgent need for more effective diagnostic tools and therapeutic strategies to improve patient outcomes [3].

Early diagnosis is critical in the management of AD. Evidence indicates that cognitive decline can precede the onset of overt clinical symptoms by several years. Detecting the disease in its early stages allows clinicians to initiate interventions that may prolong independence and enhance quality of life for both patients and their families [4, 5]. Initiation of symptomatic treatment soon after diagnosis may also delay progression [6 - 8]. Furthermore, early diagnosis reduces the likelihood of misdiagnosis and inappropriate treatment, which are more common in later stages. It also enables patient participation in clinical trials, providing access to emerging therapies with the potential to modify disease course. Thus, early detection is essential not only for optimizing individual care but also for addressing the broader public health challenges associated with AD [9].

NEUROIMAGING'S ROLE IN DIAGNOSING ALZHEIMER'S DISEASE

Neuroimaging provides essential information on the structural and functional alterations of the brain in Alzheimer's Disease (AD). Fig. (**1**) illustrates the major neuroimaging modalities—Computed Tomography (CT), Magnetic Resonance Imaging (MRI), functional MRI (fMRI), positron emission tomography (PET), and Single-Photon Emission Computed Tomography (SPECT)—each of which has distinct applications in the clinical evaluation of AD. The figure also summarizes the characteristic symptoms and brain regions typically assessed by these techniques (Table **1**).

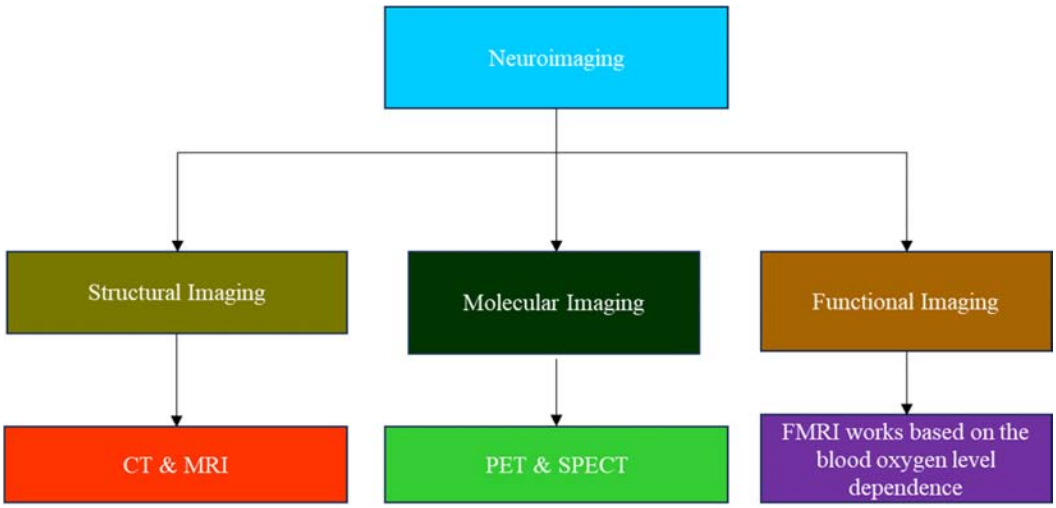

Fig. (1). Classification of neuroimaging techniques. The chart is prepared using MS PowerPoint.

Table 1. Types of neuroimaging, classifications, symptoms, and areas involved.

Neuroimaging Type	Classification	Types	Common Symptoms	Areas Involved
FMRI	Non-Invasive	Functional Imaging	Cognitive impairments, mood disorders	Prefrontal Cortex, Temporal Lobe
MRI	Non-Invasive	Functional	Memory Issues, Cognitive Deficits	Prefrontal Cortex, Temporal Lobe
CT	Non-Invasive	Structural Imaging	Confusion, Strokes, Trauma, Tumors, Dizziness	Various Brain Sites
PET	Non-Invasive	Metabolic Imaging	Alzheimer's, cancer	Hippocampus region
SPECT	Non-Invasive	Perfusion Imaging	Neurodegenerative Disorders	Various Brain Regions
DTI	Non-Invasive	Structural (White Matter)	Chronic Pain Reduction in Cognitive Ability	Anterior-Posterior Brain Regions
DWI	Non-Invasive	Diffusive Restriction Imaging	Fractional Anisotropy, Neuronal Loss, Hippocampal Atrophy	Corpus Callosum, Posterior Cingulate Cortex
NFTS	Non-Invasive	NFT Distribution and Tau Pathology Visualization	Memory and Language Impairment, Visuospatial Dysfunction, Tremors, and Hallucinations	Entorhinal Cortex, Parahippocampal Gyrus, Primary Sensor and Motor Cortex

CHAPTER 5

Digital Tools and Artificial Intelligence in Alzheimer's diagnosis

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Abstract: The integration of digital tools and Artificial Intelligence (AI) has brought significant advancements to the diagnosis of various diseases, particularly neurodegenerative disorders like Alzheimer's disease. AI, particularly Machine Learning (ML), enables the analysis of vast and complex datasets, such as neuroimaging, electronic health records, cognitive assessments, and biomarkers, which are crucial for early detection and accurate diagnosis. These technologies offer the potential to identify subtle changes in patients' conditions over time, improving the precision of diagnosis and facilitating the development of personalized treatment plans. Digital tools, including wearable devices, mobile applications, and fitness trackers, allow for continuous and passive monitoring of patient data, providing real-time insights into physiological parameters like gait, heart rate, and brain activity. These tools can detect early signs of cognitive decline and other abnormalities, aiding clinicians in making more informed decisions about disease progression. AI has demonstrated its potential in automating image analysis, identifying biomarkers, and predicting disease progression, which can expedite the diagnostic process and enhance the overall healthcare experience. Additionally, AI-driven models can integrate data from multiple sources, enabling comprehensive assessments and more accurate predictions about the onset and development of diseases like AD. However, there are several challenges associated with the widespread adoption of AI in clinical settings, such as concerns about data quality, model interpretability, ethical considerations, and cost. Overcoming these barriers is essential to ensuring that AI technologies become accessible, reliable, and effective in healthcare. This chapter explores the transformative potential of AI and digital tools in diagnostics, discussing their applications, benefits, challenges, and the future directions for improving patient care and outcomes.

Keywords: Alzheimer's disease, Artificial Intelligence, Biomarkers, Digital tools, Early diagnosis, Machine Learning, Neuroimaging.

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INTRODUCTION

Between 70 and 85% of dementia cases are caused by Alzheimer's Disease (AD), the most common neurological illness linked to dementia. Around 50 million individuals worldwide suffer from dementia at the moment, and as life expectancy rises, that figure is predicted to increase to 139 million by 2050, posing serious socioeconomic and medical issues. Cognitive deficits and gradual impairment of memory are the main characteristics of AD, including difficulties in language, spatial orientation, executive function, and behaviour, ultimately leading to a gradual loss of personal autonomy [1]. Approximately 95% of AD cases occur in individuals aged 60–65 and older, while 5% have an early onset. Key pathological features used to diagnose AD include amyloid angiopathy, tau protein-containing neurofibrillary tangles, and β-amyloid plaques. To distinguish AD from prion diseases, these plaques must stain negative for prion antibodies but positive for β-amyloid. The number of plaques and tangles in the brain must exceed that of age-matched individuals without dementia. In some cases, TDP-43 protein accumulation and Lewy bodies (alpha-synuclein aggregates) in the amygdala are also observed [2]. The incidence of AD increases with age, with women being at higher risk than men, as indicated by a European meta-analysis. AD is listed as a cause or contributing factor in many recorded deaths of affected patients. The disease progresses through stages, beginning with the absence of harmful Aβ species, advancing to normal cognition with Aβ deposition, and eventually leading to neurodegeneration [3]. Key pathogenic features of AD include amyloid-beta (Aβ) plaque buildup, neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau proteins, synaptic dysfunction, and neuronal death. The Amyloid Precursor Protein (APP) cleaves abnormally, forming Aβ plaques that impair neuronal communication and trigger neuroinflammation. Tau proteins cause microtubule instability, leading to neuronal death. Cognitive decline is further exacerbated by oxidative stress and persistent neuroinflammation, contributing to neuronal damage. The cholinergic theory underscores how the depletion of acetylcholine and the death of cholinergic neurons impair memory and learning. Early synaptic loss, which is closely linked to cognitive symptoms, is a hallmark of AD [4, 5].

Current therapies for Alzheimer's disease focus on symptom management rather than changing the severity of the condition. Memantine and cholinesterase inhibitors are two medications that can improve memory and alertness, but do not increase life expectancy or decrease illness development. Lifestyle improvements, such as diet and exercise, are advised as first-line therapies because they have the potential to lower Alzheimer's risk and delay cognitive decline. Although limited therapeutic trials have yielded encouraging outcomes, larger research is needed to

validate the pathological hallmarks of Alzheimer's disease (Fig. **1**), such as Aβ and phosphorylated tau. Although there is evidence that early detection of AD pathology can enhance treatment results, large-scale clinical studies are still required [6].

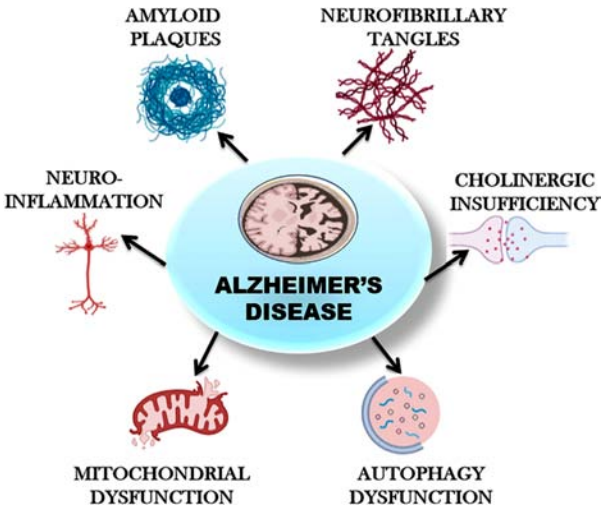

Fig. (1). Pathophysiology of alzheimer's disease [5] (Designed by Canva).

With growing healthcare expenditures, healthcare practitioners have been motivated to discover efficient methods for early detection and treatment of this degenerative neurological condition. Early brain abnormalities, including β-amyloid build-up and cell alterations, can develop during the preclinical period, even without clinical symptoms. Biological markers detected in cerebrospinal fluid (CSF) are used to identify whether a patient's condition has advanced to this stage. AD dementia is defined in several ways depending on the presence and certainty of clinical symptoms. It is described as a significant cognitive impairment that interferes with daily activities. Biomarkers such as reduced glucose absorption, lowering β-amyloid peptide levels, rising tau protein levels in CSF, and temporal lobe atrophy on magnetic resonance imaging can help identify Alzheimer's dementia more precisely [7].

TRADITIONAL *VS.* DIGITAL BIOMARKERS: ADVANCING ALZHEIMER'S DIAGNOSIS

Current diagnostic methods for Alzheimer's disease (AD) primarily rely on neurocognitive assessments, brain imaging techniques, and CSF analysis. In patients with AD, brain pathology often reveals amyloid plaque deposition, neurofibrillary tangles, and notable synapse loss. Diagnostic guidelines emphasize

CHAPTER 6

Natural Products and Phytochemicals in Alzheimer's Management

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Abstract: Alzheimer's Disease (AD) is a progressive neurodegenerative condition that primarily impairs memory, cognition, and behavioural functions. Since no definitive cure currently exists, increasing attention has shifted toward lifestyle interventions and nutraceutical supplementation as supportive strategies for prevention and symptom management. Nutraceuticals such as polyphenols, omega-3 fatty acids, antioxidants, and vitamins have shown promise in alleviating oxidative stress, neuronal inflammation, and age-related neurodegeneration processes strongly implicated in AD pathology. Compounds like curcumin, resveratrol, and docosahexaenoic acid (DHA) have demonstrated neuroprotective properties in preclinical and clinical studies, suggesting their potential in moderating cognitive decline and supporting brain health. Lifestyle-based approaches, including regular physical activity, cognitive exercises, and dietary modifications, further enhance protective outcomes. Exercise promotes neuroplasticity, optimises cognitive performance, and reduces dementia risk, while social engagement and mental stimulation strengthen resilience to cognitive impairment. Nutritional patterns such as the Mediterranean diet, rich in plant-based foods and healthy fats, are associated with a reduced risk of developing AD, highlighting the significant role of diet in maintaining neural function. Although ongoing research continues to explore optimal doses, duration, and mechanisms of these approaches, integrating nutraceuticals with lifestyle modifications offers a practical and holistic strategy to delay or minimise AD progression and improve quality of life in at-risk individuals.

Keywords: Alzheimer's disease, Antioxidants, Cognition, Exercise, Mediterranean diet, Nutraceuticals.

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INTRODUCTION

Neurodegenerative disorders (NDD) are a group of conditions characterised by selective dysfunction and progressive loss of neurons, neuroglial cells, and neural pathways in the spinal cord and Central Nervous System (CNS) [1]. There are several types of NDDS based on their key clinical features, such as dementia, Parkinsonism [2], and Huntington's disease [3, 4]. Alzheimer's Disease (AD), the most prominent category of dementia in older people, is characterised by a progressive loss of memory and other cognitive functions [5, 6]. Cognitive impairment is one of the most common clinical manifestations of this disease [7, 8]. Amyloid beta (Aβ) and cholinergic hypotheses are the two leading theories for AD. Other risk factors include vascular illnesses, infections, ageing, head trauma, genetic disorders, and variables in the environment [8, 9]. Recent studies have shown that the repression of hyperphosphorylation of tau protein, accumulation of Aβ plaque, inflammatory responses, and unfolded protein reactions, as well as the reduction of oxidative injury and biological targets such as beta secretase (BACE-1), cholinesterase, and monoamine oxidase (MAO), have a significant impact on the genesis of AD [10].

Approximately 5 million new instances of AD are discovered each year, making it the most well-known and prevalent form of dementia, comprising 60 to 70% of all cases. Globally, there are already more than 50 million dementia patients, and by 2050, that Figure is expected to double, with AD accounting for the majority of cases [11, 12]. Compared to other nations worldwide, AD-related fatalities are more common in Libya, Lebanon, and Finland.

Many pathogenic mechanisms interact intricately to form the pathophysiology of AD. Extracellular accumulation of Aβ, anomalies in tau protein, oxidative destruction of neurons, intracellular neurofibrillary tangles (NFTs), neuronal inflammation, mutations in genes, dysregulation of neurotransmitters, and other molecular and cellular mechanisms are significant variables in AD, as represented in Fig. (**1**). The primary cause of AD is an extracellular aggregation of Aβ plaques, which causes neurotoxicity and finally leads to neuronal cell death [13 - 15].

The extracellular aggregation of Aβ significantly influences the pathophysiology of AD. The breakdown of Amyloid-β Protein Precursor (APP) yields Aβ peptides, which can subsequently unite to form insoluble plaques. These plaques cause inflammation and interfere with regular neural activity. Intermediate forms of Aβ accumulation, known as Aβ oligomers, are very detrimental to neurons and are implicated in neurotoxic cascades and synaptic malfunction. Anomalies of the tau protein contribute to the formation of intracellular NFTs. Tau (τ) is a microtubule-

linked protein that helps preserve the shape and movement of neurons. Due to hyperphosphorylation, tau in AD detaches from microtubules and aggregates form NFTs. These tangles impede axonal transit, damage neurons, and cause cognitive impairment.

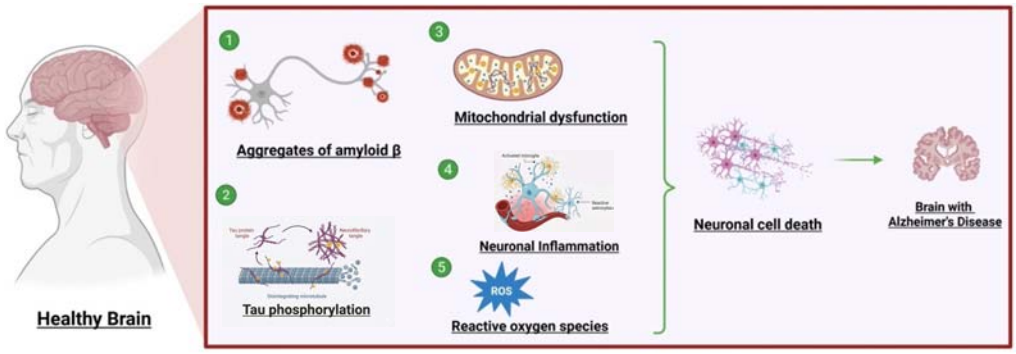

Fig. (1). Diagrammatic representative view of the pathophysiology of alzheimer's disease (Created by BioRender.com).

One important aspect of the pathophysiology of AD is oxidative stress. Overproduction of Reactive Oxygen Species (ROS) compromises antioxidant defences, ultimately resulting in oxidative neuronal injury. ROS are produced by oxidative stress caused by Aβ, inflammation, and mitochondrial impairment. Lipid oxidation, DNA damage, protein oxidation, and mitochondrial impairment are all consequences of oxidative stress, which exacerbates synaptic abnormalities and neuronal cell damage.

A significant contributing factor to AD is neuronal inflammation. The aggregation of Aβ and the formation of NFTs stimulate the activation of microglial cells, the brain's defence cells. Proinflammatory cytokines generated by activated microglia have been connected to tau pathology, formation of Aβ, and neuronal cell injury. Neuroinflammation is exacerbated by the selection of peripheral immune cells, which intensifies the inflammatory response.

AD research has focused on new pathways and mechanisms. New research focuses on the gut-brain axis, mitochondrial dysfunction, vascular anomalies, and epigenetic mutations. Mitochondrial impairment increases the risk of oxidative stress and affects energy production. Reduced cerebral blood flow and metabolic issues are caused by vascular anomalies (Fig. **1**). Gene expression patterns are influenced by epigenetic changes, which may contribute to the progression of AD. The pathogenesis of dementia has been linked to the gut-brain axis, which involves a bilateral interaction between gut bacteria and the brain [16, 17].

CHAPTER 7

Various Immunotherapy and Targeted Therapeutics for Managing Alzheimer's Disease

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Abstract: Globally, Alzheimer's Disease (AD) is the most common neurological disorder that affects the older population. However, the intricacy of AD pathophysiology causes disparities in our knowledge of the disease and could be the primary cause of the medication development failure for AD. Thankfully, several preclinical and clinical research projects are still in progress, which will continue to pave the way for the discovery of disease processes and direct approaches to AD diagnosis and medication development. For instance, because of the exceptional preclinical outcomes, immunotherapeutic approaches targeting the tau and amyloid-β (Aβ) proteins were originally thought to be almost successful in clinical treatment. This strategy has been called into question due to the numerous failures in clinical studies involving vaccinations and humanized anti-tau monoclonal, anti-Aβ antibodies. However, immunotherapy targeting Aβ may still have potential, as evidenced by the United States Food and Drug Administration (USFDA) recent endorsement of Aducanumab, a novel anti-Aβ monoclonal antibody. Immunotherapies targeting various targets, including microglia, tau, and the gut-brain axis, are also being developed in the meantime. To improve the accuracy and efficacy of immunotherapeutic treatments, more inspection is required to clarify the targeted proteins' structures and epitopes. In this review, we concentrate on the mechanisms of action of immunotherapies focused on microglia, tau, and Aβ in AD. We also discuss current developments and prospects for immunotherapeutic approaches to AD.

Keywords: Alzheimer's disease, Antibody, Drug development, Immunotherapy, Vaccine.

INTRODUCTION

The leading cause of dementia in the elderly is Alzheimer's disease (AD). Its pathological hallmarks include neurofibrillary tangles with hyperphosphorylated

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tau and extracellular amyloid-β (Aβ) plaques [1, 2]. Clinically, memory loss and cognitive decline are the primary indicators [3]. AD typically manifests after the age of 65, affecting 5–10% of adults in this age group, and rising to nearly 50% among individuals above 85 years [4]. Patients usually experience progressive dementia, mobility difficulties, and eventually succumb 5–12 years after onset [5].

Both controllable and non-modifiable risk factors contribute to AD pathology. Lifestyle-related disorders such as cardiovascular diseases, diabetes, and hypertension are among the modifiable ones [6 - 9]. Current treatments, namely cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, provide only symptomatic relief and do not slow disease progression [10, 11]. Thus, disease-modifying strategies are urgently needed.

Considerable research has focused on the Aβ hypothesis, which suggests that reducing Aβ production, preventing aggregation, or enhancing its clearance could alter disease progression. Vaccination and passive immunization with antibodies have shown promise, while other approaches target tau protein and microglia-mediated immune pathways (*e.g.*, TLRs, TREM2) [12 - 15].

Both active and passive immunotherapies present distinct advantages and limitations. Active immunization (vaccines) stimulates cellular and humoral immune responses, producing endogenous antibodies for prolonged periods at relatively low cost and with fewer injections. However, older patients may respond less effectively. Passive immunotherapy, in contrast, involves direct administration of antibodies, allowing more controlled dosing and the option to halt treatment if adverse effects occur. Yet both approaches carry risks of excessive immune activation, including cerebral vasculitis [16].

Anti-Aβ immunotherapies remain at the forefront of clinical research. These therapies primarily function by decreasing Aβ synthesis, inhibiting its aggregation, and enhancing clearance [17 - 19]. Although many candidate agents have been tested for reducing Aβ burden, most have failed to demonstrate meaningful clinical benefit, raising doubts about whether Aβ remains the optimal therapeutic target.

Nevertheless, Aβ accumulation is still considered a central driver of neurodegeneration, and enhancing its clearance continues to be an area of interest [20 - 24]. Active immunization with Aβ or its fragments has been shown to trigger endogenous antibody production [25]. The landmark 1999 study demonstrated that full-length Aβ immunization reduced plaque deposition in PDAPP mice [26]. This led to the development of AN1792, the first Aβ vaccine tested in humans, but clinical trials were halted after 6% of participants developed T cell-mediated meningoencephalitis [27, 28].

Second-generation vaccines, such as CAD106, were designed without the T-lymphocyte epitope to minimize overactive immune responses. While active immunotherapy offers the benefit of generating long-lasting antibodies with short-term treatment, it also carries unpredictable risks, particularly in elderly populations.

Table **1** and Fig. (**1**) illustrate some of the recent developments in the creation of active immunotherapy for AD. Humanized monoclonal antibodies and polyclonal immunoglobulins have been employed in passive immunotherapy to enhance Aβ clearance because of the limited reactivity of vaccinations & the development of T cell-dependent adverse responses [29]. Although passive immunotherapy guarantees reasonably stable antibody titers, it is typically associated with numerous negative adverse consequences, like cerebral amyloid angiopathy with microhaemorrhages and vasogenic edema. Antibodies affect the secondary structure of monomers of Aβ, preventing them from aggregating into oligomers or fibrils. They help antigen-antibody complexes pass through the blood-brain barrier through interactions with Fc receptors; they promote opsonization of the antigen, which triggers complement activation and subsequent macrophage phagocytosis; and they lower peripheral Aβ levels, which may enhance the central nervous system's Aβ outflow. These are some of the well-known mechanisms of passive immunization [29 - 33].

Table 1. Treatment approaches that target tau in the creation of AD medications.

Therapeutic Strategy	Compound	Sponsor	Mechanism	Population	Route of Administration	Phase of development	Clinical trial identifier	Status
Active immunotherapy	AN1792	Janssen/Pfizer	Vaccination	mild to moderate AD	intramuscular	II	NCT00021723	discontinue
	amilomotide (CAD106)	Novartis	Vaccination	Individuals at risk of developing clinical symptoms of AD	intramuscular	II/III	NCT02565511	discontinue
	UB-311	United Neuroscience	Vaccination	mild AD mild AD	IM	II II	NCT02551809 NCT03531710	Completed discontinue
	ABvac40	Araclon Biotech	Vaccination	participants having extremely mild AD or amnestic mild cognitive impairment	SC	II	NCT03461276	discontinue

CHAPTER 8

Gene Therapy and RNA-Based Innovations for Management of Alziemer's

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Abstract: Gene therapy is the process of transferring genetic material to treat a disease or, at the very least, to enhance a patient's clinical condition. Gene therapy can be implemented by transforming viruses into genetic carriers that deliver the desired gene to the target cells. Depending on the kind of genome, these vectors can be classified as either DNA-based or RNA-based viral vectors. Gene therapy holds promise for treating illnesses that traditional medicine cannot address. To apply it, a patient's cells must receive one or more nucleic acids or a faulty gene. Clinical gene therapy has advanced significantly during the past ten years. One can list several noteworthy achievements, including the development of medicines for diabetes, Alzheimer's, Parkinson's, cystic fibrosis, and several types of cancer. Long-term studies on the therapy of Alzheimer's disease have led to the development of various drugs, such as monoclonal antibodies to Aβ aggregation, cholinesterase inhibitors, and inhibitors of tau aggregation. Researchers continued to work on the disease even though the drugs did not stop its advancement, and as a result, gene therapy, a recently developed, state-of-the-art technique for delivering genes to specific locations where they can express the desired functionalities, is being introduced. For AD, gene therapy is a promising disease-modifying treatment. "Protein-coding and noncoding RNAs make up between 70 and 90 percent of the human genome. These RNAs are the primary determinants of biological variation in cells and populations. Among the different kinds of nucleic acids, RNA is more adaptable than DNA because of its single-stranded structure, direct protein-encoding capability, and high degree of modification for specific regulatory and therapeutic uses. Even with its bright future in biomedicine, RNA-based therapy still has several obstacles to overcome. Notably, delivering RNA effectively and precisely while reducing immunological reactions is one of the biggest technical challenges. Viral vectors, Virus-Like Particles (VLPs), lipid nanoparticles (LNPs), and Extracellular Vesicles (EVs) are some of the methods that have been created for delivering RNA.

Keywords: Biopolymers, Encoded molecules, Germline, Immune response, Innovative therapy, Lipid nanoparticles, RNA delivery systems, Somatic cells, Transcriptions, Viral vectors.

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INTRODUCTION

Through the continuous calls for eventual treatments targeting diseases at the molecular level, the gene therapy field has managed to demonstrate considerable relative successes. It is now a generally accepted notion that these early successes are indeed likely to pave the path for a more constant drive for better prospects through not only appreciation and comprehension of the various obstacles standing in the way of efficient in vivo gene delivery but also by the judicious development of ad hoc technologies [1, 2]. Furthermore, the therapeutic work in the field of gene therapy has triggered additional spin-offs, like the development of accurate in vivo imaging methods. Indeed, a significant number of innovations capitalizing on gene expression are envisaged [3, 4].

In the rapidly evolving field of antisense and gene repair technology, the gap that once existed has now significantly narrowed between the numerous in vitro successes and the actual therapeutic applications that employ either cell in vivo or whole living organisms. Recent advancements in RNA interference have further accelerated the research aimed at bespoke modulation of gene function, uncovering possibilities for targeted interventions. The prospects in these areas appear to be quite encouraging and promising [5]. Currently, the new generations of RNA interference inhibitors are still in their early stages of development, but as these innovative technologies emerge, the full extent of their therapeutic capabilities will likely expand considerably [6]. The gene delivery aspect of this technology might also reflect similar developments in its unique manner, given the intense level of dynamism that characterizes this field. Indeed, considering that we have merely begun to scratch the surface of understanding how much more efficient, selective, targeted, or localized gene delivery could become, there are numerous encouraging and compelling hypotheses in progress. These ideas are simply awaiting validation, and their potential impact on medical science may be profound as we continue to unveil new methodologies and technologies in this exciting domain of research [7].

OVERVIEW OF GENE THERAPY

Gene therapy refers to the delivery and stable introduction of new genetic information into a cell to obtain a therapeutic benefit. Therapy based on gene manipulation has the potential to radically change how we treat life-threatening diseases [8, 9]. Gene therapy focused on delivering a functioning copy of a defective gene to correct a monogenic disorder, by gene augmentation, is now well into the ongoing clinical phase for a variety of genetic disorders. In recent years, knowledge of disease-causing mutations has increased exponentially,

offering the possibility of correlating mutations to certain protein functions that aid in the definition of the path of disease. For some of the many genetic diseases for which the gene and mutation cause is known, there is already a defined sequence of events of disease progression, which could provide a predictive roadmap for therapeutic intervention [10, 11].

One of the properties of gene therapy that makes it attractive is the potential for a single administration of the therapeutic gene and its product. The ideal goal of gene therapy is to deliver a therapeutic payload without the requirement for modifying the host's genome, ensuring the long-term presence of the correctable defect protein. For monogenic diseases, this would parallel the most advantageous feature of protein replacement therapy [12]. The actuality of current vector technology, however, is that the gene is not specifically targeted to the appropriate tissue to maximize effectiveness; the gene is often not integrated in an expression-efficient site, and long-term expression is largely not achieved. In an attempt to develop a positive profile record of gene therapy, somatic cell gene therapy trials have begun, and results are being reported. In another approach, strategies attempting to obtain a particular pharmacological effect rather than full correction of the disease by gene therapy are being pursued by isolating or inhibiting RNA transcription of relevant gene sequences. Optimal results in systemic genetic manipulation in humans, however, remain objectives rather than accomplishments. Fig. (**1**) depicts gene therapy-based methods and RNA-based innovations used in the diagnosis and treatment [13].

EVOLUTION OF RNA-BASED INNOVATIONS

Recently, nature has been exploited to achieve highly proficient tools capable of effectively interfacing with a variety of biological systems. The first part of this overview outlines the evolutionary and progressive increases in knowledge of a very promising group of biotechnological tools: RNA-based molecules. These naturally occurring molecules interact with proteins to carry out enzymatic as well as regulatory biological functions, providing a conceptual framework for the development of RNAs as biotechnological tools. The second part of this overview summarizes some pioneering applications of RNA technologies in biotechnological and biomedical fields [14]. Genomes are made up of DNA and RNA, and the study of the regulation of genome expression, as well as the functional properties of regulatory RNA-based molecules, has been pivotal in the development of efficient, easy, and flexible RNA-based tools [15]. These tools provide a powerful toolkit of biotechnological instruments that have proved to be optimized and straightforward, therefore having a wide impact in investigations related to functional genomics, systems biology, and evolution. Furthermore, they

CHAPTER 9

Comorbidities and their Impact on Disease Progression: Focused on Alzheimer's Disease

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Abstract: Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that primarily affects cognitive and functional abilities. While much study has focused on the basic pathology of AD, the role of comorbidities in influencing its progression has gained increasing attention. Comorbidities, such as cardiovascular diseases, diabetes, depression, and sleep disorders, are highly prevalent in individuals with AD and significantly impact its trajectory, outcomes, and management. This chapter focuses on the intricate interplay between Alzheimer's disease and common comorbid conditions, highlighting how these comorbidities contribute to faster cognitive decline, worsened behavioral symptoms, and increased caregiver burden. Key mechanisms linking comorbidities to AD progression, including chronic inflammation, vascular dysfunction, metabolic dysregulation, and oxidative stress, are discussed in detail. These processes increase neuronal damage and can accelerate the formation of amyloid-beta and tau proteins, indicators of AD pathology. The chapter also addresses the clinical challenges posed by comorbidities in AD patients, such as diagnostic complexities, polypharmacy, and the lack of tailored management guidelines. Practical strategies for effective management are outlined, including comprehensive assessments, personalized care plans, and the merging of pharmacological and non-pharmacological treatments. The role of multidisciplinary teams in optimizing patient outcomes is emphasized, along with emerging research into novel therapeutic targets and biomarkers for early detection and intervention. This chapter aims to provide a significant resource for healthcare practitioners, researchers, and caregivers, promoting a more complete approach to managing Alzheimer's disease in the presence of comorbidities.

Keywords: Alzheimer's disease, Biomarkers, Cognitive decline, Comorbidities, Integrated care, Metabolic disorders, Vascular dysfunction.

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INTRODUCTION

Comorbidities are defined as the coexistence of one or more chronic medical conditions alongside a primary disease, and they play a critical role in determining the course, management, and prognosis of patients [1, 2]. Their presence often complicates therapeutic strategies, as the interaction between multiple disease processes can produce synergistic or antagonistic effects, leading to increased morbidity and reduced treatment effectiveness.

In the context of Alzheimer's Disease (AD), a progressive neurodegenerative disorder primarily driven by the accumulation of amyloid-beta plaques and neurofibrillary tangles in the brain [3], comorbidities are especially significant. AD is the leading cause of dementia worldwide, with prevalence rising sharply with advancing age, and is associated with profound cognitive deficits, behavioral alterations, and impaired ability to perform activities of daily living [4, 5]. These clinical manifestations not only compromise the quality of life of patients but also place a substantial burden on caregivers and healthcare systems.

Due to the aging process and the systemic effects of neurodegeneration, patients with AD are particularly vulnerable to comorbid conditions [6]. Common examples include metabolic disorders such as diabetes mellitus, cardiovascular diseases such as hypertension and stroke, and neuropsychiatric illnesses including depression and anxiety [7]. These comorbidities do not occur in isolation but often interact with the underlying neurodegenerative pathology, thereby accelerating cognitive decline, worsening functional impairment, and complicating pharmacological as well as non-pharmacological management.

Importance of Understanding the Interplay between Comorbidities and AD Progression

AD is rarely an isolated condition. Most patients with AD have multiple comorbidities that can either contribute to the onset of dementia or exacerbate cognitive and functional decline. The presence of these conditions complicates disease management in several ways:

- **Acceleration of Cognitive Decline:** Most comorbidities, including diabetes, hypertension, and depression, contribute to a high risk of the development of dementia and accelerated progression of cognitive impairment. Chronic systemic inflammation, oxidative stress, and vascular dysfunction are key mechanisms linking these conditions to AD pathology.
- **Increased Burden of Symptoms:** Comorbidities can worsen behavioral and psychological symptoms of dementia like agitation, depression, and sleep

disturbances, which result in a higher requirement for medical procedures and social services.

- **Complications in Diagnosis and Management:** The presence of overlapping symptoms between AD and comorbid conditions poses challenges in diagnosis. For instance, cognitive impairment in AD may be worsened by uncontrolled diabetes, making it more difficult to determine the primary cause of cognitive dysfunction. Additionally, polypharmacy—commonly required to manage multiple chronic diseases—raises the risk of adverse drug interactions and further cognitive deterioration.
- **Increased Mortality and Morbidity:** Most of the studies suggest that AD patients with multiple comorbidities have a greater mortality rate than those without. Cardiovascular diseases, infections, and metabolic disorders contribute to poorer survival outcomes, highlighting the need for a holistic treatment approach.
- **Impact on Caregivers and Healthcare Systems:** The presence of comorbidities increases the complexity of care, leading to higher caregiver burden and healthcare costs. The need for frequent medical visits, hospitalizations, and specialized care can overwhelm both family caregivers and healthcare professionals [8 - 10].

Objectives and Scope of the Chapter

The main aim of this chapter is to provide a comprehensive knowledge of the role of comorbidities in AD progression by exploring their prevalence, underlying mechanisms, and impact on cognitive and functional decline. It seeks to define and classify common comorbid conditions, including metabolic, cardiovascular, neurological, infectious, and psychiatric disorders, while examining how these conditions accelerate AD pathology through mechanisms such as systemic inflammation, oxidative stress, vascular dysfunction, and metabolic dysregulation. Additionally, the chapter will analyze the consequences of comorbidities on disease outcomes, including faster cognitive deterioration, increased behavioral symptoms, reduced treatment efficacy, higher caregiver burden, and increased mortality rates. A critical focus will be on the challenges in diagnosing and managing comorbidities in AD due to symptom overlap, polypharmacy risks, and the lack of standardized treatment guidelines. Also, the chapter will offer effective management strategies, emphasizing personalized care plans, pharmacological and non-pharmacological interventions, and the role of multidisciplinary healthcare teams in providing integrated care. Finally, the chapter points out future research, such as advances in biomarker identification and new therapeutic strategies, to counteract the effects of comorbid conditions on AD progression. Through these discussions, the chapter seeks to inform healthcare providers,

CHAPTER 10

Emerging Pharmacological Innovation in Alzheimer's Treatment

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Abstract: Alzheimer's disease is a complicated neurological disease characterized by behavioural defects, memory loss, and progressive cognitive deterioration. Recent developments in pharmaceutical innovation have demonstrated promise in tackling fundamental pathogenic pathways, such as neuroinflammation, synaptic dysfunction, mitochondrial impairments, amyloid-\u03B2 and more. Notable strategies include synapse-restoring medicines, tau aggregation inhibitors, neuroinflammatory modulators, and monoclonal antibodies that target amyloid-β2 aggregates. Therapeutic possibilities are further enhanced by emerging methods such as gene editing and RNA-based therapeutics, as well as biomarkers for personalized medicine. These developments provide fresh optimism for altering the course of the disease and enhancing patient outcomes, even though issues like safety profiles and efficient delivery methods still exist. While tau aggregation inhibitors and anti-tau antibodies are being studied to reduce the formation of neurofibrillary tangles, monoclonal antibodies such as aducanumab and lecanemab have shown potential in reducing the amyloid plaque burden. Neuroinflammation is a key player in the widespread pathology of Alzheimer's disease, and drugs that alter microglial activity or stop pro-inflammatory cytokines such as TNF-α and IL-1β are used to combat it. Due to growing understanding of the meaning of mitochondrial dysfunction, mitophagy activators and mitochondrial protectants have been developed to preserve the energy balance of neurons. Gene and RNA-based therapies may hold promise for precision medicine, including CRISPR/Cas9 editing and antisense oligonucleotide platforms that allow us to correct protein expression and genetic factors to more precisely address genetic and phenotypic variables. Moreover, advances in imaging and fluid biomarkers are enabling more personalized treatment plans and improved early detection. Though challenges still remain, including in managing side effects and delivering medications across the blood-brain barrier, these developments represent a significant breakthrough

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in the fight against Alzheimer's. Future efforts must prioritize cross-disciplinary approaches integrating lifestyle shifts with pharmaceutical advancements to enable complete illness remediation.

Keywords: Alzheimer's disease, Diagnosis, Emerging innovation, Gene therapy, Tau aggregation inhibitors, Treatment.

INTRODUCTION

Alzheimer's disease is a neurological illness and the most prevalent kind of dementia. Currently, an estimated 50 million individuals globally experience some types of dementia; nevertheless, as the lifespan rate increases, this figure is predicted to rise by 2050. Alzheimer's Disease (AD) entails deficits in memory, mental problems, changes in behaviour and loss of individual autonomy. AD is characterized by both histopathological features, such as abnormally phosphorylated tau protein, which contributes to the development of Neurofibrillary Tangled Structures (NFTs) in the cortex of the brain and subcortical gray matter, and outside the cell aggregates of β-amyloid peptides (Aβ) fibrils, resulting in neuritic plaques [1, 2]. Endogenous "damage signals" like Aβ oligomers may activate microglial cells, thereby leading to the secretion of cytokines that are pro-inflammatory. It, in turn, causes signaling pathways in neurons, leading to hyperphosphorylation and Tau protein aggregation. As neurons die, this protein develops, which stimulates the microglial cells and leads to neurodegeneration. Alzheimer's disease has been classified as either sporadic or familial. Among them, familial is Early-Onset Alzheimer's Disease (EOAD) in people below 65 years of age. This class is marked by mutations in certain genes, including the presenilin 1 gene (PSEN1, 14q24.2), as well as the presenilin 2 gene (PSEN2, 1q 42.13), and the amyloid precursor protein gene (APP, 21q 21.3), which has been found to be present in up to 70% of cases of familial Alzheimer disease [3 - 5]. However, on the other hand, sporadic AD occurs in people older than 65 years of age. Stress, depression, environmental exposure, social exclusion, poor academic achievement, traumatic brain injury, and metabolic syndrome have been identified as important risk factors for sporadic AD [6].

By 2050, the total number of instances of dementia is predicted to reach two to three times, with Alzheimer's disease accounting for the vast majority. In Latin America, as in other regions, with low incomes, the challenge is not only a spike in the percentage of people suffering from dementia, but also a shortage of investment in health professionals and training and epidemiological studies, which strengthens chronic barriers related to resources, culture and stigma [7]. Genetics was at the forefront of many advances that have assisted scientists in

comprehending AD. Conversely, advancement in developing medications for managing Alzheimer's disease has yet to be achieved. All authorized medications treat symptoms, and there is no reliable proof that any may delay the progression of illness [8].

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

Amyloid β and neurofibrillary tangles in the hippocampus are two of the most noticeable morphological characteristics of Alzheimer's disease. Given the abundance of accounts of idiopathic and familial AD, this condition can be generally classified as either Familial AD (FAD) or Sporadic AD (SAD), with the build-up of mostly neurofibrillary tangles and amyloid β in the hippocampus. In FAD, it is linked to alterations in PSEN1, PSEN2 and APP, while in SAD, it is linked to age, genetics, metabolism, and environment. A detailed understanding of the pathophysiology of AD is extremely important in the use of therapeutic regimens. Different hypotheses have been investigated, and a multitude of mechanisms have been considered to provide a better insight into the pathophysiology of AD [9].

There are different types of genes that influence Alzheimer's disease progression by the development of amyloid plaque, tau pathology and neuroinflammation. These genes and their molecular mechanism for the progression of Alzheimer's disease are given in Table **1** [8, 9].

Table 1. Genes involved in the progression of Alzheimer's disease.

Gene	Pharmacological function	Molecular pathways in AD	References
ADAM10 (15q21.3)	It is the primary secretase in the brain, contributing to the non-amyloidogenic route of APP metabolism.	Changes in APP metabolism (by the non-amyloidogenic route), synaptic plasticity and hippocampal neurogenesis.	[10, 11]
BIN1 (2q14.3)	Participates in immunological reactions, calcium balance, apoptosis, synaptic vesicle endocytosis, and plasma membrane dynamics	Assists in amyloid (by secretase activity) and Tau disease, and is linked to inflammatory processes, apoptosis and calcium equilibrium.	[12, 13]
EPHA1 (7q34)	It contributes to synaptic formation and plasticity by regulating cell migration, angiogenesis and death.	Mutations in immunological pathways, endocytosis and breakdown of the blood-brain barrier.	[14]
CD33 (19q 13.3)	It inhibits immune cell activity and cytokine synthesis	Influences the activation of microglial (neuroinflammation) and Aβ elimination *via* microglial cells	[15]
TOMM40 (19q13.32)	Helps stabilize the mitochondrial membrane respiratory chain	Impairment of the mitochondrial membrane leads to oxidative stress	[16]

CHAPTER 11

Recent Advances in Drug Development for the Management of Alzheimer's Disease

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Abstract: Alzheimer's disease is a long-term, neurodegenerative disease of the brain, which is a major cause of dementia affecting the elderly population. It is also characterised by behavioural dysfunction and cognitive impairment. Alzheimer's disease is a complex disease involving multiple genetic and environmental risk factors. Despite significant advancements in the study of Alzheimer's disease, many aspects of the disease are still poorly understood. Although a reduction in acetylcholine and the formation of amyloid-beta plaques are characteristic signs of Alzheimer's disease, the precise causes and mechanisms underlying the illness are still unknown. Significant reduction of neurotransmitters, such as acetylcholine and butyrylcholine, and aggregation of β-amyloid protein in the neocortex of the brain are strongly linked to the etiology of Alzheimer's disease. Although there is currently no treatment for Alzheimer's, both pharmaceutical and non-pharmacological therapy options are being thoroughly studied. Recent research has introduced promising new drugs designed to address the root causes of AD. Acetylcholinesterase inhibitors (*e.g.*, donepezil) and NMDA receptor antagonists (*e.g.*, memantine) are used for symptomatic relief. Donepezil was the first cholinesterase inhibitor drug approved for the symptomatic treatment of Alzheimer's disease. Later, other drugs, such as rivastigmine and galantamine, also got FDA approval. Newly FDA-approved drugs, such as Aducanumab and Lecanemab, have been effective in reducing amyloid plaques. Many hybrid molecules targeting two or more relevant sites of disease have been developed and tested. These hybrid compounds showed antiinflammatory and amyloid aggregation inhibition. Additionally, many global clinical trials are underway testing effective therapies for Alzheimer's disease. Current therapies can control symptoms, but they cannot halt or reverse the disease's course. Researchers are now focusing on target the molecular mechanisms that underlie Alzheimer's disease. This chapter examines the most recent therapeutic approaches targeted at amyloid plaques, tau protein tangles, neurotransmitter imbalances, anneuro inflammation.

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Keywords: Acetylcholine, Alzheimer's, β-amyloid, Dementia, Donepezil, FDA, Galantamine, NMDA, Rivastigmine.

INTRODUCTION

Alzheimer's Disease (AD) is the most common type of neurodegenerative disorder, marked by a steady deterioration of memory and cognitive function. Effective treatments for this deadly condition remain elusive despite a great deal of research since its discovery in 1906 [1]. The pathophysiology of AD includes dysfunction in cholinergic neurotransmission, aggregation of Aβ protein, accumulation and phosphorylation of tau, and involvement of inflammatory and oxidative pathways [2]. These findings contributed to clinical trial design, therapeutic target development, and current knowledge of AD etiology. There is a global need for effective treatments, as illustrated by the extensive pipeline of medications that have been studied but have not yet demonstrated disease-modifying effects. The FDA has granted approval for only four small-molecule drugs for the management of AD: galantamine, donepezil, and rivastigmine (all cholinesterase inhibitors) and memantine, which is an *N*-methyl-D-aspartate receptor inhibitor [3].

Significant reduction of enzymes, such as acetylcholine, in the neocortex of the brain is strongly associated with AD. Preventing the acetylcholine degradation by acetylcholinesterase enzyme in the brain can improve cholinergic neurotransmission, which is a treatment approach for this disease [4]. In 1993, the FDA approved Tacrine (Cognex) as the first acetylcholinesterase inhibitor (AChEI) to treat Alzheimer's disease (Fig. **1**). However, Tacrine's toxicity to the liver led to its removal from the market in 2013 [5], and Donepezil (**2**), rivastigmine (**3**), and galantamine (**4**) are examples of second-generation AChEIs that are more selective. As first-line medications for AD, they demonstrated better pharmacokinetic profiles or fewer side effects. Furthermore, AChEI, such as donepezil (**2**) and galantamine (**4**), may result in unexpected effects when used in combination with other neurologic medications, metal chelators, or antioxidants [6, 7]. *N*-Methyl-D-Aspartate (NMDA) receptors are involved in glutamate signaling in the brain. Over-activation of NMDA receptors may result in damage to neurons. This takes place in several neurological illnesses, including AD. Memantine (**5**) is an FDA-approved antagonist of the NMDA receptor, which is used to treat moderate to severe AD stages [8]. It regulates the transfer of glutamate and is effective in enhancing patients' behavior, everyday life skills, and cognitive performance. For patients with moderate to severe AD, Namzaric (**6**, fixed dose combination of memantine (**5**) extended release and donepezil (**4**) offers an additional therapeutic alternative [9].

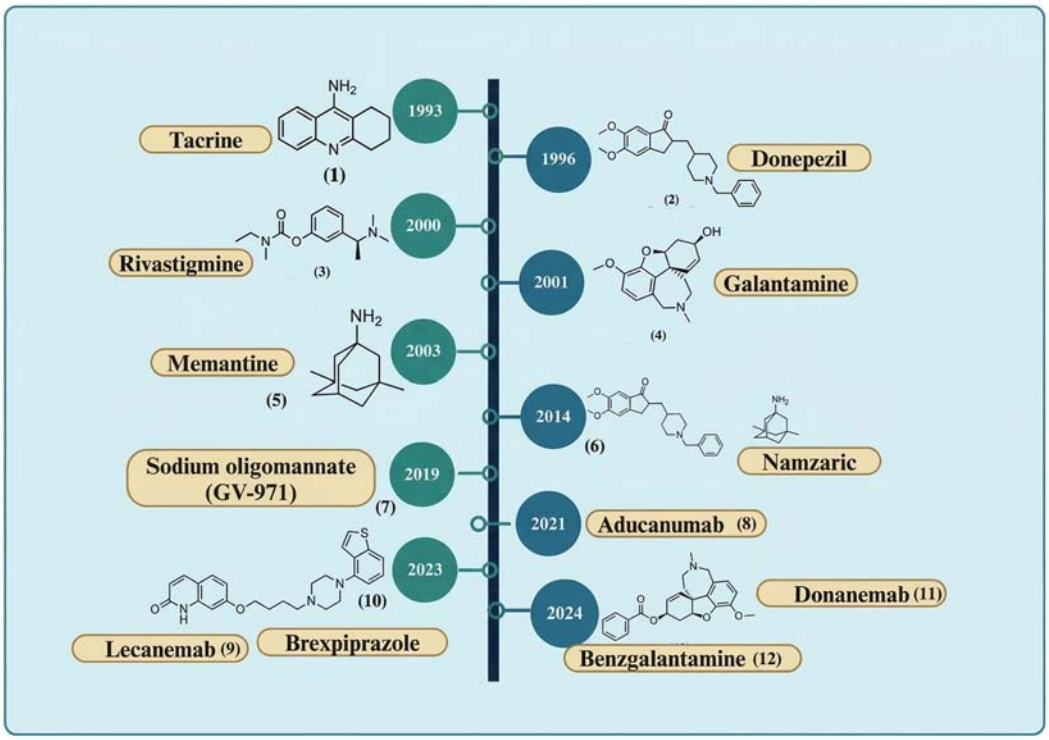

Fig. (1). Timeline of FDA/China authorised drugs for Alzheimer's disease.

Sodium oligomannate (**7**, GV-971) was provisionally approved in 2019 [10]. GV-971 is derived from a marine algae. It was hypothesized that sodium oligomannate (**7**, GV-971) would prevent AD by preventing neuroinflammation induced due to dysbiosis of the gut and inhibiting Aβ fibril production [11]. To further investigate its efficacy and safety, phase four clinical trials (NCT05058040 and NCT05181475) are underway, with an anticipated ongoing until 2025.

The monoclonal antibodies, such as aducanumab (**8**) and lecanemab (**9**), that target Aβ exhibited promising results. Aducanumab (**8**) won FDA approval in 2021. Aducanumab (**8**) targets both insoluble fibrils and soluble oligomers [12]. More soluble Aβ aggregates (oligomers and protofibrils) were bound by lecanemab (**9**) [13]. Lecanemab (**9**) obtained traditional approval in 2023 [14]. Despite the risks and costs associated with amyloid-related imaging abnormalities, all these monoclonal antibody treatments have been shown to effectively remove Aβ plaque and prevent cognitive decline. Brexpiprazole (**10**) targets norepinephrine, dopamine, and serotonin receptors and is frequently used for schizophrenia and depression. It has been shown to lessen agitation in AD patients [15].

CHAPTER 12

Intranasal Drug Delivery in Treating Alzheimer's Disease

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Abstract: Alzheimer's disease is a monogenic brain illness that impairs thinking, remembrance, judgment, and focus, making it difficult for an individual to carry out regular responsibilities. Drug delivery to the brain is necessary for the effective treatment of diseases of the CNS, including epilepsy, schizophrenia, meningitis, migraine, Parkinson's disease, and Alzheimer's disease. However, because the Blood-Brain Barrier (BBB) separates the Central Nervous System (CNS) from the rest of the body, this remains a challenging area to manage. The blood-brain barrier and additional barriers to oral and other routes, such as decreased bioavailability, quick metabolism, rapid excretion, and drug breakdown by enzymes and stomach juices, make it difficult to transfer drugs to the brain. Promising drug delivery strategies for the efficient nasal delivery of anti-Alzheimer medications with enhanced permeability and bioavailability include lipid particle systems, emulsion-based systems, vesicular drug delivery systems, and other nanocarriers. Effective and targeted drug administration via the nasal route is influenced by charge, size, neurotherapeutic type, and formulation excipients. One of the cutting-edge approaches to brain targeting being explored to overcome the limitations of oral and other modes of administration is the nose-to-brain medication delivery device. A promising substitute for administering medications and enhancing the therapy of Alzheimer's disease is the intranasal route, through the olfactory and trigeminal pathways in the nasal cavity. Intranasal delivery provides a direct channel to the brain. Nasal physiology, however, can restrict bioavailability and impede drug absorption. Despite being limited by the particular circumstances of the

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nasal canal, intranasal administration has become a viable option. Using nanotechnology-based nano-carriers for intranasal delivery is a novel strategy. By offering increased bioavailability, greater permeability, efficient blood-brain barrier traversal, prolonged retention inside the body, and precise brain targeting, this approach may be able to get past the present restrictions. Therefore, it is necessary to use technical solutions to maximize the physicochemical features of formulations.

Keywords: Alzheimer's disease, Blood-brain barrier, Intranasal administration, Lipid particulate systems, Novel approaches.

INTRODUCTION

People over 65 are typically affected by Alzheimer's Disease (AD). As the number of senior people rises, the disease's prevalence has gone up [1]. Although this has prompted more research into potential cures, the illness still has no proven cure [2, 3]. Studies have tested over 200 therapeutic agents, and since 2003, the FDA has not approved a new medication for the treatment of the condition [4, 5]. The failure of the applied treatments has been the subject of numerous conjectures. The most significant is misinterpreting the etiology of AD and selecting the incorrect primary treatment objectives [6]. According to research, the brain's distinctive tau nodes and amyloid plaques are a result rather than a cause. Alzheimer's disease is the outcome of improper brain trauma repair and neuroinflammation [7]. Cognitive and behavioral impairments are the outcome of this neurological condition. Acetylcholinesterase inhibitor medications, for example, are poorly soluble, have a low bioavailability, and cannot cross the blood-brain barrier, making them ineffective in many cases [8]. The intranasal approach is highlighted by these drawbacks of the existing treatment. This approach appears to be a viable way to transport medications to the brain [9]. Instead of using parenteral or oral methods, recent research looks at the direct intranasal delivery of pharmacological groups to the CNS.

THE USE OF INTRANASAL DRUG ADMINISTRATION IN ALZHEIMER'S DISEASE TREATMENT

Substitute for parenteral and oral methods. Given that the trigeminal and olfactory nerve cells are in close proximity to the peripheral and central nervous systems, intranasal administration is a non-invasive technique that permits medications to pass through the BBB (Blood-Brain Barrier). Drugs can enter the brain directly from the respiratory epithelium and olfactory area [10, 11]. Thus, the focus is on treating neurological problems [12]. Rapid onset of action, avoidance of the presystemic metabolism of the liver and intestines, decreased systemic exposure, direct administration to the brain and cerebrospinal fluid (CSF), simplicity of use, and improved patient compliance are some benefits when compared to alternative

drug administration routes. Limitations of this route include weak nasal permeability and mucociliary clearance [13]. Studies demonstrate that drugs administered into the nasal cavity must have a longer residence time to overcome nasal mucociliary clearance [14].

Drugs are transported either extracellularly or intracellularly across the nasal barriers. Endocytosis is the initial stage of intranasal transport to trigeminal ganglion cells and olfactory sensory neurons, in that order [15]. Agents may not reach the central nervous system for up to 24 hours following nasal delivery due to its extreme slowness [16]. After that, intracellular transport takes place to the brainstem and olfactory bulb. Both passive diffusion and receptor-mediated endocytosis can cause transcytosis between the basolateral membrane and the intracellular space. Diffusion *via* the extracellular channel linked to olfaction into the olfactory bulb takes approximately 0.73 to 2.3 hours. The duration of diffusion into the brainstem is roughly 17–56 hours; substances obtained through this channel are transferred to the blood, olfactory mucosa, and ultimately the central nervous system. This method depends on the drug's size and molecular weight and is less efficient than the transcellular route [17]. On the other hand, this technique is quicker and enables the delivery of low molecular weight medications to the central nervous system in minutes [18].

Mucociliary clearance allows nasal medications to be removed from the nasal cavity. The medication that enters the bloodstream can be eliminated via regular clearance processes or could allow the BBB to enter the brain. Ensuring appropriate therapeutic amounts of medication distribution to target brain regions is the difficult part of the application. Targeting the right receptors in the brain is essential for treating CNS conditions like Parkinson's disease, schizophrenia, AD, brain tumors, meningitis, and migraines. Frey introduced this technique in 1989 to treat AD and other CNS illnesses, and it shows promise in providing current medications and compounds for alternative therapies in AD.

Mucociliary clearance enables the removal of nasal medications from the nasal cavity. It is possible to remove the medication that enters the bloodstream using either regular clearance processes or by crossing the blood-brain barrier. Making sure that the target parts of the brain receive therapeutically appropriate quantities of medication delivery is the difficult part of the application. For the treatment of CNS disorders such as Parkinson's disease, schizophrenia, AD, brain tumors, meningitis, and migraine, the drug's location in the brain must target the essential receptors. Frey introduced this technique in 1989 to treat AD and other CNS illnesses, and it shows promise in providing current medications and compounds for alternative therapies in AD [19].

CHAPTER 13

Case Studies and Patents in Alzheimer's Disease Research

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Abstract: Alzheimer's disease is a progressive neurodegenerative disorder that affects cognition, memory, and neuronal loss. Treatment strategies remain largely underdeveloped, despite numerous studies. The chapter reviews the most recent case studies and patents to further novel therapeutic approaches in the treatment of AD. Case studies can depict the potential to exemplify the patient's response in the course of such therapy, where personal treatment choices are considered in conjunction with the efficacy of newly introduced therapies. Patents are the indicators of innovative drug discovery, biomarkers, and neuroprotective strategies. We focus on patents covering Multi-Target Directed Ligands (MTDLs), monoclonal antibodies, and small molecules targeting amyloid-beta (Aβ) and tau proteins. We also scan patents centered around cholinesterase inhibitors, neuroinflammation modulators, and techniques in gene therapy. Case studies that involve success stories of drug development in clinical settings, along with personalized medicine approaches, are also examined. New biotechnological interventions like drug delivery systems *via* nanotechnology and AI-based diagnostic tools are emerging to transform AD treatment. Furthermore, regulatory policies and intellectual property rights also create an atmosphere conducive to speeding or slowing the commercialization of innovative products for AD. Within view, this chapter gives an integrated view of current patents with a case study of the management of AD concerning their real-world applications, as well as current discoveries in its management.

Keywords: Alzheimer's disease, Amyloid-beta, Artificial intelligence, Biomarkers, Case studies, Cholinesterase inhibitors, Drug discovery, Gene therapy, Neurodegeneration, Neuroinflammation, Patents, Personalized medicine, Tau protein.

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INTRODUCTION

The global incidence of dementia, particularly Alzheimer's disease, has seen a significant rise over the last thirty years. This concerning trend underscores the urgent requirement for effective intervention strategies. While various therapeutic agents have been developed to alleviate symptoms, delay onset, or even arrest or reverse the progression of this challenging condition, results to date have yielded limited success. Consequently, research and development efforts focused on this pressing issue have been expanding in response to the high demand for effective solutions. However, the low efficacy outcomes reported in numerous clinical trials have highlighted the need for coordinated and collaborative initiatives [1]. These collaborative efforts are designed to enhance knowledge sharing and promote mutual learning among diverse stakeholders, including researchers, clinicians, and organizations engaged in addressing this intricate challenge. In this context, we will examine patents and scientific publications to pinpoint the most promising constructs and strategies currently underpinning therapeutic approaches. This analysis is part of a broader strategic and forward-looking examination aimed at identifying the most effective avenues for combating dementia. Dementia itself is a syndrome composed of various conditions, all marked by a progressive decline in cognitive function, primarily affecting older adults. Among these conditions, Alzheimer's disease is the most common and recognized cause, further illustrating the complexities of this syndrome [2]. The likelihood of developing Alzheimer's disease increases sharply after the age of 60, and the association between aging and the disease's onset is concerning. For example, global life expectancy was approximately 66.4 years in 1980, whereas it now averages around 71 years. This increase in life expectancy serves as a significant risk factor for the growing prevalence of Alzheimer's disease, as it also reduces the risk of mortality from other, more prevalent causes. This situation highlights the critical need for continued research and innovative approaches to better understand Alzheimer's disease and to develop effective strategies to mitigate its substantial impact on individuals and society as a whole [3].

UNDERSTANDING AD

As the world's population ages, the prevalence of chronic neurodegenerative diseases such as Alzheimer's disease becomes an urgent health concern for society. Early and accurate diagnosis is essential for timely and effective intervention; however, most conventional diagnostic methods have limited effectiveness in early diagnosis [4]. To find effective biomarkers for early diagnosis of Alzheimer's disease, researchers investigate the applications of patents and publications in Alzheimer's disease research. In this entry, two case

studies are presented: (1) the application analysis of Alzheimer's disease patents based on a database; and (2) a general introduction to the Alzheimer's disease research literature, followed by an example showing how to analyze the co-occurrence of keywords in Alzheimer's disease research. Together with the previous chapter, we hope it will provide a good basis for patent- and literature-based research on Alzheimer's disease. Fig. (**1**) depicts the features analyzed in the post-mortem brain for the treatment of AD with the help of different available information after case studies [5, 6].

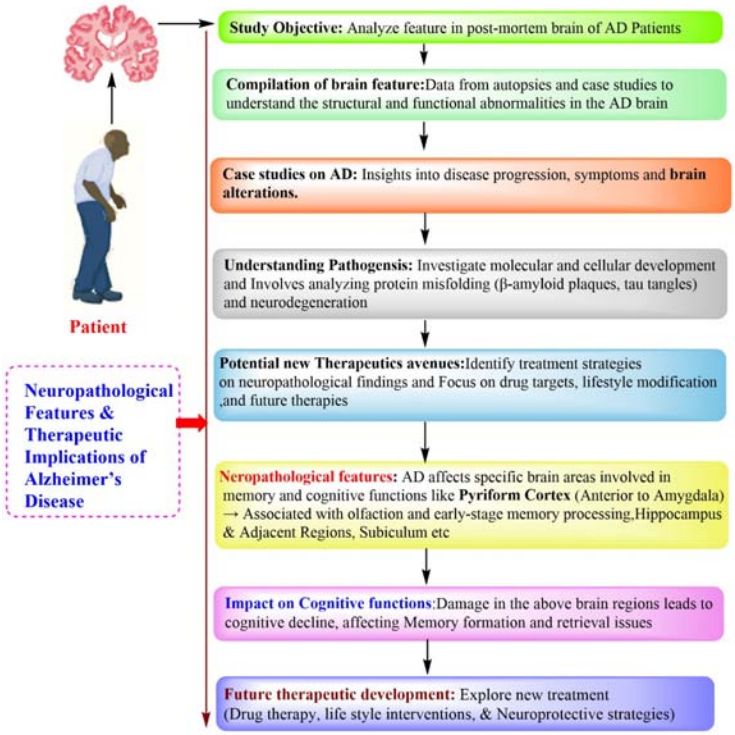

Fig. (1). Depicts a treatment strategy for AD through a case.

Alzheimer's disease is the most common form of dementia. Pathological features include the formation of senile plaques and neurofibrillary tangles in the brain. To diagnose Alzheimer's disease, one must identify two types of basic lesions, which are amyloid deposits and neurofibrillary tangles. Amyloid deposits are mainly amyloid βA4 protein, and this defect is particularly useful in diagnosing Alzheimer's disease histopathologically [7, 8]. However, this is usually only done in autopsies. Alzheimer's disease is not just a natural decline in cognitive function but involves multiple cognitive dysfunctions. As a neurodegenerative disease, the most prominent clinical manifestation is a decline in cognitive function. In terms

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Prashant Kumar Dhakad

Dr. Prashant Kumar Dhakad is a Professor of Pharmacology at Gyan Vihar School of Pharmacy, Suresh Gyan Vihar University, Jaipur, India. He holds a Ph.D. in Pharmacy and has over 14 years of experience in teaching, research, and academic administration. His research interests include cardiovascular pharmacology, neuropharmacology, metabolic and inflammatory disorders, wound healing, and herbal therapeutics. He has authored more than 50 peer-reviewed publications in SCI, SCOPUS, and Web of Science–indexed journals, published multiple academic books, and holds several granted and published patents. He is a recipient of research and academic excellence awards, has supervised postgraduate and doctoral scholars, and actively contributes to curriculum development, accreditation, and quality assurance in higher education.

Raghav Mishra

Dr. Raghav Mishra with over 14 years of academic and research experience in Pharmaceutical Sciences complemented by industrial exposure, Dr. Raghav Mishra holds a Ph.D. in Pharmacy and a Gold Medal in M. Pharm. (Pharmaceutical Chemistry). His background reflects a strong foundation in both research and professional practice. His research expertise spans synthetic chemistry, structure–activity relationship studies, and in silico approaches for drug discovery. Dr. Mishra has published more than 60 research papers in reputed international and national journals, along with three books, four patents, and many conference presentations. His contributions have earned him significant recognition, with over 1,200 citations, an h-index of 15, and inclusion among top-cited authors in the Journal of Heterocyclic Chemistry. In addition to his academic achievements, Dr. Mishra has been honored with multiple awards for excellence in teaching, research, and innovation, including recognition from Wiley, GLA University, and the Shri S. L. Nasa award from Lloyd Institute of Management and Technology. He is also an active reviewer and editorial board member for several reputed scientific journals.

Shweta Sharma

Dr. Shweta Sharma, Associate Professor, Department of Pharmaceutical Chemistry, IIMT College of Pharmacy, India, holds a Doctorate in Pharmaceutical Chemistry from Jamia Hamdard University, New Delhi, specializing in synthetic chemistry, bioinformatics, AI, NGS-driven studies and public health. With a distinguished career, Dr. Sharma boasts numerous publications in international journals, solidifying her reputation as a leading scientist and recipient of prestigious research excellence awards. Her academic journey encompasses one and a half year of teaching experience coupled with two years of impactful contribution at the Indian Council of Medical Research (ICMR) in WHO funded project. In addition, she had industrial experience in Formulation and development and QC for 2 years in renowned pharmaceutical companies.

Sudhanshu Mishra

Mr. Sudhanshu Mishra is an academician and researcher in Pharmaceutical Sciences specializing in pharmaceutics and advanced drug delivery systems. He is currently serving as an Assistant Professor at the Faculty of Pharmaceutical Sciences, Mahayogi Gorakhnath University Gorakhpur. He holds an M.Pharm (Pharmaceutics) degree and is pursuing a Ph.D. from Dr. APJ Abdul Kalam Technical University, Lucknow. With over four years of teaching and research experience, he has contributed extensively to nanotechnology-based drug delivery, herbal therapeutics, and digital healthcare applications. Dr. Mishra has authored numerous research papers, book chapters, and edited books published in reputed indexed journals and international publishers. He is a recipient of the Young Scientist Award and has actively participated in national and international academic conferences.

Nishant Kumar Gaur

Nishant Kumar Gaur is an Assistant Professor at the Lloyd School of Pharmacy and an enthusiastic researcher in pharmaceutical sciences. He holds a B. Pharm from Oxford College of Pharmacy, Ghaziabad, and an M. Pharm in Pharmaceutics from Galgotias University, and is currently pursuing a Ph.D. at Amity Institute of Pharmacy, Noida. With experience in both academia and industry, he has taught and conducted research in advanced drug delivery systems, nanotechnology, and analytical methods. He has also worked with Integral Biosciences and Mankind Pharma, gaining expertise in LC-MS/MS, method validation, and regulated lab practices. His work spans research publications, patents, and student mentorship.