1. Introduction

1.1. Alzheimer's disease

The brain is the most crucial organ in the human body. It controls and coordinates every action and reaction, permits us to think and feel, and enables us to have feelings and memories, all the things that make us human. Weighing in at 1400 grams, a spongy mass of fat and protein is made up of two principal types of cells called neurons and glia each numbering in billions. Additionally, it is made up of special protective layer consist of tightly bound cells that function as a semi-permeable gate, i.e., blood-brain barrier (BBB). It maintains the brain atmosphere safe from toxins and harmful substances entering through normal blood circulation. Aging and oxidative stress are key aspects that caused neuronal damage/ degeneration in the brain. Neurodegeneration is a feature of many other debilitating, incurable diseases that are rapidly rising viz. Alzheimer's disease (AD) and Parkinson's disease (PD) [1]. The diseases represent an intriguing burden to global population. These age-dependent disorders are becoming increasingly prevalent, in part because the elderly population has increased in recent years. Effective therapeutic approaches are dreadfully required, but it would be possible only with intense comprehension of pathological conditions and mechanism of the disease.

Cognitive deficits occur not only in AD, but also in vascular dementia, frontotemporal dementia (FTD), mixed dementia, and dementia with Lewy bodies (LBD). The pyramidal and extrapyramidal systems are affected by amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Parkinson's disease (PD), and spinocerebellar ataxias (SCAs) [1]. Despite their multiple clinical events, reflecting the loss of neurons and synapses in distinct brain regions, these diseases share common features and pathways. One such mechanism is the aggregation of nuclear or cytosolic proteins. These include beta-amyloid (Aβ) plaques and inclusions of hyperphosphorylated tau in AD and other tauopathies, aggregates of α-synuclein in PD and

other synucleinopathies, inclusions of TAR DNA-binding protein (TDP)-43 in ALS and FTD, and polyglutamine protein aggregates in HD and other CAG-polyglutamine repeat diseases [2]. Abnormalities in protein conformations and their cellular and neuroanatomical distribution establish the major histopathologic features that are essential in making a specific neuropathologic diagnosis [3].

AD is acknowledged as a progressive multi-factorial neurodegenerative disorder, that leads to the progressive loss of functional, mental, and behavioral decline. The disease progresses symptomatically from mild to severe and found its place among the eight topmost health complications worldwide. One of the upsetting aspects of AD is the loss of cognitive abilities which currently accounts for 50 million cases worldwide and the proportion of deaths related to AD is going up [4]. The extensive challenge which AD possesses to healthcare system makes it as crucial for researchers to develop new therapeutic strategies to fight this disease.

1.2. Status of research and development

1.2.1. International status

Worldwide more than 55 million people suffering from dementia, 60 % of whom reside in low and middle-income nations [5]. Approximately 10 million new cases are reported every year. The most prevalent form of dementia is Alzheimer's disease may be a factor in 60–70 % of cases. Dementia is one of the major causes of disability and dependency among older people and the sixth leading cause of death. Globally, dementia cost economies 1.3 trillion US dollars in 2019. Around half of these expenses are related to informal careers (such as family members and close friends), who devote an average of 5 hours per day to care and supervision. Both directly and indirectly, dementia has an outsized impact on women [5]. Women provide 70 % of the care hours for dementia patients, but they also have shorter disability-adjusted life years and higher mortality rates owing to dementia.

1.2.2. National status

The prevalence of dementia in India is expected to increase by 197 % by 2050 and is highly systemic and societal [5]. Due to a lack of knowledge in society, poor literacy rates, the perception that dementia is a natural part of aging, and a lack of adequate healthcare, the treatment gap for dementia is currently estimated to be greater than 90%. Delays in receiving medical care result from the belief that dementia is a normal progression of age-related weakness. Socio-cultural circumstances affect how people see dementia, the tales they tell, and the language they use to describe its symptoms. Social presumptions regarding gender, social class, religion, economic status, and personal biographies in the setting of families also have an impact on this understanding. As a result, stigma persists at a high level and frequently discourages people from seeking treatment or support, which causes social isolation. There is little knowledge of dementia, not even among healthcare experts [5]. Previous reports suggested that there is a systemic lack of knowledge about dementia care even after diagnosis, which results in insufficient post-diagnosis support.

Pharmacological and non-pharmacological therapies that lessen symptoms and enhance quality of life are used to manage dementia. The majority of medications used to treat symptoms are broadly accessible, but they are also expensive and only partially accessible to those with poor socioeconomic status. A few non-pharmacological therapeutic approaches are used; however, it is difficult to create a standardized cognitive stimulation therapy (CST) regimen because of sociocultural and educational variance. Culturally appropriate activities included in the CST include singing bhajans, painting rangoli or Kolam patterns, or playing traditional Indian games. India has traditionally accepted Ayurveda as a tailored form of holistic healing. Focus is placed on developing an evidence base for traditional treatments that provide qualitative change for illnesses like dementia, with significant push supplied by the

Government of India through the AYUSH initiative and more recently, the Traditional Medicine initiative of the World Health Organization [6].

1.3. Symptoms

The noticeable early symptoms of AD include memory loss with difficulty in recalling things, i.e., recent events, visits, or discussions. As the disease progresses, forgetfulness or memory lapse such as repetitive questioning, forgetting appointments, misplacing things, cannot find a way to a familiar place, etc. becomes frequent. The patient is unable to focus, develops reduced thinking ability, poor multitasking performance, falls in reasoning ability and judgment, and declined performance in known and familiar tasks [1]. The other neuro-psychiatric symptoms of the disease include apathy, irritability, mood swings, social withdrawal, aggression, suspicion of others, delusion, wandering, changes in the sleep cycle and insomnia, etc. AD causes a high burden of suffering to patients, their families, and caregivers [3].

1.4. Diagnosis of Alzheimer's disease

The Alzheimer's association suggests a few guidelines for the diagnosis of AD. The diagnostic test involves a physical examination, followed by a neurological examination such as testing the body reflexes, muscle coordination and strength, sensation, and eyeball movement. Further testing is performed by a mental examination, viz. Mini-Cog test and mini-mental state exam (MSME) [7]. A Mini-Cog test involves completion of the two tasks:

a. A patient is made to remember the name of three objects, and after a certain time, it is asked to repeat the name.
b. In the second test, the patient is made to draw a clock with all 12 numbers and asked to indicate a time specified.

The results of the examination indicate that whether there is need for a further investigation or not.

Depression and mood assessment tests are also carried out to diagnose the other symptoms present in AD. Brain imaging through magnetic resonance imaging (MRI) or computed tomography (CT) is recommended to further access the underlying cause of dementia. In some instances, dementia may be due to tumor, stroke, or trauma but not AD. Florbetapir, florbetaben, and flutemetamol are amyloid-specific positron emission tomography (PET) ligands that are employed for the diagnosis of AD pathology [7]. The other tests also involve estimation of $A\beta_{42}$, hyperphosphorylated tau (p-tau), and total tau protein in cerebrospinal fluid.

1.5. Pathophysiology

Since the time of Dr. Alois Alzheimer, worldwide, neuropathologists have recognized Aβ plaques and neurofibrillary tangles (NFTs) in the autopsied brains of AD patients, signifying that these pathologies are the root causes of AD [8]. These plaques damage /disrupt the synapse and neuronal circuits. Numerous hypotheses have been established based on the various contributing factors to study of this multifactorial disorder, such as the cholinergic hypothesis, Aβ hypothesis, tau hypothesis, and inflammation hypothesis. Cholinergic neurons are highly essential for function of brain and maintenance of excitation-inhibition balance within neural circuits [8]. Although cholinergic neurons are distributed in various discrete regions, they can project to almost all parts of the brain. These cells release a neurotransmitter called acetylcholine (ACh), which plays crucial role in the regulation of sensory functions, behavioral flexibility, and associative learning. In AD, there is marked deficiency of ACh due to atrophy and degeneration of subcortical cholinergic neurons, mainly those present in basal forebrain, that provides cholinergic innervation to the whole cerebral cortex [9].

1.6. Current clinical drugs for the management of AD

To date, established treatments are only for symptomatic relief, trying to equalize the neurotransmitter disturbance of the disease. Few cholinesterase inhibitors (CIs) are approved for the treatment of mild to moderate AD (Table 1.1) [9]. A further therapeutic option available for moderate to severe AD is memantine [10]. At the same time, antipsychotic and antidepressant treatments are used for the behavioral symptoms of the disease. Tacrine, a competitive acetylcholinesterase inhibitor (AChEI) and the first drug to be approved for use in AD by the US-FDA in 1993 was withdrawn from the market in 2013 due to the high incidence of side effects, mostly derived from hepatotoxicity.

DPZ is a reversible noncompetitive CI approved for treatment of AD and is currently the most commonly prescribed drug for the treatment of AD [11]. DPZ is extremely selective for AChE over BuChE activity (405:1). Compared to other approved AChEI, DPZ is similarly effective in improving cognitive and functional decline in AD with comparable safety and tolerability. Rivastigmine, a non-selective pseudo-reversible ChE inhibitor, has been reported to have fewer side effects as well as positive benefits after administration to mild to moderate AD patients (Table 1.1). Galantamine, a weak competitive reversible AChEI is also a potent allosteric modulator of nicotinic acetylcholine receptors in certain areas of the brain and potentiates the effects of orthosteric agonists [12]. Recently, Aducanumab and Lecanemab are approved in the US as disease-modifying agents in AD [13].

The rationale for creating semi-synthetic derivatives of vasicine is to modify and improve its pharmacological properties for specific therapeutic purposes. Here are some key reasons for developing semi-synthetic derivatives of vasicine:

1. Enhanced pharmacological activity: The natural compound vasicine may have limited bioavailability or specific pharmacological effects. By modifying its chemical structure

through semi-synthesis, it is possible to enhance its pharmacological activity, making it more effective in treating certain medical conditions.

2. Optimizing drug delivery: Semi-synthetic derivatives can be designed to improve drug delivery and bioavailability. This can be achieved by altering the chemical structure to enhance solubility, stability, and absorption, which can lead to better therapeutic outcomes.

3. Targeting specific receptors or pathways: Semi-synthetic derivatives can be tailored to target specific receptors or biological pathways involved in a particular disease or condition. This targeted approach can improve efficacy and reduce off-target effects.

4. Dose optimization: Semi-synthesis allows for the creation of derivatives with different pharmacokinetic profiles. This can be useful for optimizing the dosing regimen, ensuring that the drug achieves therapeutic levels in the body and maintains those levels over time.

5. Commercial viability: The development of semi-synthetic derivatives can make a compound more commercially viable by improving its manufacturing process and making it cost-effective to produce.

The lack of therapeutic effectiveness of the currently available drugs based on the single target paradigm for the treatment of AD prompted the search for multi-target directed ligands (MTDLs), designed by various modern medicinal chemistry approaches of different pharmacophoric moieties from well-known bioactive molecules, able to bind to multiple targets associated with AD.

Table 1.1. List of currently available medications for the management of Alzheimer's disease

Drug name	Drug type and use	How it works	Common side effects	References

Lecanemab	Disease-modifying immunotherapy prescribed to treat mild cognitive impairment or mild Alzheimer's	Removes abnormal beta-amyloid to help reduce the number of plaques in the brain	Amyloid-related imaging abnormalities (ARIA), headache, cough, diarrhea, nausea, high blood pressure, low blood pressure, and low oxygen	[14]
Aducanumab	Disease-modifying immunotherapy prescribed to treat mild cognitive impairment or mild Alzheimer's	Removes abnormal beta-amyloid to help reduce the number of plaques in the brain	ARIA, which can lead to fluid buildup or bleeding in the brain; headache, dizziness, falls, diarrhea, confusion	[15]
Donepezil	Cholinesterase inhibitor prescribed to treat symptoms of mild, moderate, and severe Alzheimer's	Prevents the breakdown of acetylcholine in the brain	Nausea, vomiting, diarrhea, muscle cramps, fatigue, weight loss	[16]
Rivastigmine	Cholinesterase inhibitor prescribed to treat symptoms of mild, moderate, and severe Alzheimer's	Prevents the breakdown of acetylcholine and butyrylcholine (a brain chemical similar to acetylcholine) in the brain	Nausea, vomiting, diarrhea, weight loss, indigestion, muscle weakness	[17]
Memantine	N-methyl D-aspartate (NMDA) antagonist prescribed to treat symptoms of moderate to severe Alzheimer's	Blocks the toxic effects associated with excess glutamate and regulates glutamate activation	Dizziness, headache, diarrhea, constipation, confusion	[18]
Combination of memantine and donepezil	NMDA antagonist and cholinesterase inhibitor prescribed to treat symptoms of moderate to severe Alzheimer's	Blocks the toxic effects associated with excess glutamate and prevents the breakdown of acetylcholine in the brain	Headache, nausea, vomiting, diarrhea, dizziness, anorexia	[18]
Galantamine	Cholinesterase inhibitor prescribed to treat symptoms of mild to moderate Alzheimer's	Prevents the breakdown of acetylcholine and stimulates nicotinic receptors to release more acetylcholine in the brain	Nausea, vomiting, diarrhea, decreased appetite, dizziness, headache	[19]