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International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Systemic Review on Management of Alzheimer's Disease

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DOI: https://doi.org/10.55248/gengpi.4.423.38127

A B S T R A C T

Alzheimer disease is uncurable and irreversible neurological disorder in which death of brain cells cause memory loss and thinking skills. Alzheimer disease is also known as dementia among older people of age group 65. It is clinical syndrome characterised by a cluster of symptoms, signs and stages such as mild, moderate and severe AD. Investigation and diagnosis of Alzheimer disease include instigation of pharmacological and non-pharmacological treatment of therapy. The global burden of AD is expected to accelerated from 26.6 M cases in 2006 to 106.8 M 2050.currently there are two standard pharmacotherapies exist for AD. That is approved by food and drug administration (FDA) are respectively acetyl-cholinesterase inhibitor such as: rivastigmine, galantamine, tacrine donepezil, N-methyl D-aspirate salt antagonist (NMDA)-memantine. Alzheimer disease is also treated by herbal drug such as: Ashwagandha, Brahmi, Haldi, Brahmi, Chandan, Bhilawa, etc.

Keywords: Alzheimer's disease, stages, herbal treatment, diagnosis, medicines used in AD.

Introduction

Here Alzheimer disease is a progressive impairment of membranes and cognitive functions and ultimate decline of memory loss. Alzheimer disease is caused by the development of senile plaques, which is responsible for neuronal destruction and accumulation of Beta Amyloid and synovial tangles formation. These tangles are also helping in the destruction of normal neuron. Because these tangles tiger the inflammation in the brain and progressively this inflammation is caused by neuronal atrophy, which is responsible for the death of nerve cell [1]. Alzheimer disease (AD) is one of the greatest medical care challenges of our century and is the main cause of dementia. In total, 40million people are estimated to suffer from dementia throughout the world, and this number is supposed to become twice as much every 20years, until approximately 2050 [2].

Alzheimer's disease (AD) (named after the German psychiatric Alois Alzheimer) is the most common type of dementia and can be defined as a slowly progressive neurodegenerative disease characterized by neurotic plaques and neurofibrillary tangles as a result of amyloid-beta peptide's (Aβ) accumulation in the most affected area of the brain, the medial temporal lobe and neocortical structures. Alois Alzheimer noticed a presence of amyloid plaques and a massive loss of neurons while examining the brain of his first patient that suffered from memory loss and change of personality before dying and described the condition as a serious disease of the cerebral cortex [3].

The NINDS scientists made their discoveries through a unique line of scientific reasoning. Most scientists who study Alzheimer's disease concentrate on the fibrillary tangles and amyloid plaques prevalent in the brain tissues of those with this disease. Currently there are no medicine that can slow the progression of AD. However, four FDA approved medications are used to treat AD symptoms. These drugs help individuals to carry out the activities of daily living by maintaining thinking, memory or speaking skills. They can also help with some of the behavioural and personality changes associated with AD [4].

Pathophysiology

Mainly 4 changes in the brain structure define Alzheimer Disease

1. Cortical atrophy
2. Degradation of cholinergic and other neurons
3. Presence of neuro-fibrillary tangles (NFt's)

Beta Amyloid protein and apolipoprotein E are two proteins that contribute to the genesis of the NFT's and NP's (Table 2) which are considered the signature lesions of Alzheimer Disease [1].

Differential Features Between NTFs and NPs [1].

Neuro Fibrillary Tangles (NTFs)	**Neurotic Plaque (NPs)**
These are present in normal brain mainly hippocampus amygdale cerebral cortex	They are extra cellular lesions present in the brain and cerebral vasculature.
These are located intra-cellularly within the cytoplasm of neurons	Plaque are compressed of core of beta Amyloid proteins surrounded by axon and dendrite projections of neuron
These are comprised of paired neuro-filaments adopting a helical shape which appears like tiny flame filling the neuronal cell bodies. Its presence disturbs the cell structure and its functions and finally causes cell death.	They interfere with neural transmission pathway

Alzheimer's disease is characterized by loss of neurons and synapses in the subcortical regions and cerebral cortex. This loss results in gross atrophy of the affected regions, including degeneration in the parietal lobe & temporal lobe & parts of the frontal cortex & Cingulate gyrus. Studies using MRI & PET have documented reductions in the size of specific brain regions in patients as they progressed from mild cognitive impairment in AD &in comparison with similar images from healthy older adults. Both amyloid plaques & neurofibrillary tangles are clearly visible by microscopy in brains of these afflicted by AD. plaques are dense, mostly insoluble deposits of amyloid β-peptide and cellular material outside and around neurons. Tangles are aggregated of the microtubule associated protein tau which has become hyperphosphorylated and accumulate inside the cell themselves [4].

Diagnosis

A patient suspected to have AD should undergo several tests, including neurological examination, magnetic resonance imaging (MRI) for neurons, laboratory examinations such as vitamin B12, and other tests besides the medical and family history of the patients. Vitamin (vit.) B12 deficiency has been long known for its association with neurologic problems and increasing risks of AD, according to some studies [3].

Clinical Evaluation for Diagnosis—The 2014 US Preventive Services Task Force indicated that there was insufficient evidence to evaluate the balance of benefits and harms for universal screening for cognitive impairment using formal screening instruments in community-dwelling adults age 65 years and older. While the Task Force concluded that adequate evidence existed for some screening tools that have sufficiently high sensitivity and specificity for identifying dementia, there is no published evidence of the effect of screening on decision making or planning by patients, clinicians, or caregivers. However, report of memory complaints or rapidly-progressive cognitive problems over several months may indicate an underlying medical condition that warrants further evaluation with cognitive, laboratory, and other tests. The history remains the most important diagnostic tool and should be obtained from both the patient and a close family member or friend. While some patients complain of forgetfulness, others are unable to recall details of their history and in some instances have anosognosia (i.e., lack of insight into one's disease). One clue that a patient has a memory problem occurs when the person accompanying them provides the medical history. The history should characterize the nature, magnitude, and course of cognitive changes. The neurologic examination evaluates for objective evidence of neurocognitive problems such as aphasia, apraxia, and agnosia. Unusual behaviours, such as disinhibition with hyperorality or hypersexuality, suggest a frontotemporal dementia, which comprises a group of uncommon conditions associated with neuronal loss beginning in the frontal and/or temporal regions of the brain while other areas are relatively spared. The examination may demonstrate focal neurologic signs or parkinsonism [5].

The main components to diagnosis of Alzheimer Disease are:

1. Self-Reporting regarding symptoms too family members either friend can provide symptoms and their impact on daily routine
2. Diagnosis Alzheimer on the basis of asses, memory and thinking skills
3. Clinical test and imaging test also help them to understand the causes, stage or define the characteristic of mental illness .
4. Actually, Alzheimer diseases can be diagnosed after death, when microscopic examination or autopsy of brain done. This will help to reveals the characteristic plaque and tangles [1].

Tests: -

Several tests are performed by diagnostic too sure about AD. Dr. will perform a physical test to examine over all neural health on testing the following:

1. Reflexes
2. Muscle tone and strength
3. Ability to get up from a chair and walk across to room
4. Sense of sight and hearing
5. Coordination
6. Balance
7. Psychological status or neurological psychological testing

Doctors may perform a short mental status test to check out their memory, thinking skills; psychological function as compared with other people has similar age and education. These tests play an important role to tract the ongoing symptoms in the future [1].

- **Sign and Symptoms:-**

Memory problems are one of the first signs of AD.

❖ **Mild AD:**

In case of mild AD memory loss continues and changes in other cognitive abilities appear. Symptoms in this stage can include:

1.Getting lost.

2. Trouble handling money and paying bills.

3. Repeating questions.

4.Taking longer time than before to complete normal daily task

5. Poor judgement.

6.Mood and personality changes

❖ **ModerateAD:**

In case of moderate AD, damage occurs in areas of the brain that controls language, reasoning, sensory processing and conscious thought. Symptoms may include:

1. Increased memory loss and confusion.
2. Problems recognizing family and friends.
3. Inability to learn new things.
4. Problems coping with new situations
5. Delusions and paranoia.
6. Impulsive behavior.

❖ **Severe AD:**

People with severe AD cannot communicate and are completely dependent on others for their care. Near the end the person with AD may be in bed most or all of the time. Their symptoms often include:

1. Inability to recognize oneself or family.
2. Inability to communicate
3. Weight loss.
4. Seizures.
5. Skin infections.
6. Difficulty in swallowing.
7. Increased sleeping.
8. Lack of control of bowel and bladder [4].

❖ **Stages** [6].

Stage 1	**Stage 2**	**Stage 3**	**Stage4**
Duration of 1-3 y Minimal patient awareness of the condition Mild anomia Personality changes decreased problem solving Decreased coping with difficulty situation Emotionally lability No abstract thinking ability forgetful Loss of or poor short-term memory Speech deficits Social withdrawal	Profound memory loss Cognitive impairment-2 or more of the following: Anomia, Agnosia, apraxia aphasia Severe loss of judgement Erratic/bizarre behaviour wanders aimlessly violent outbursts	Severe impairment, all cognitive functions Physical impairment, generalized muscular rigidity Incontinent Inability to recognise family members Inability to perform basic activities of daily living	Speech, motor coordination, all memory lost Inability to recognize anyone Loss of "self"

Causes and Risk Factors of Alzheimer's Disease: -

AD has been considered a multifactorial disease associated with several risk factors (Figure 2) such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors (heavy metals, trace metals, and others). The underlying cause of pathological changes in Alzheimer's disease (Aβ, NFTs, and synaptic loss) is still unknown. Several hypotheses were proposed as a cause for AD but two of them are believed to be the main cause: some believe that an impairment in the cholinergic function is a critical risk factor for AD, while others suggest that alteration in amyloid β-protein production and processing is the main initiating factor [3].

The cause of Alzheimer's disease is unknown, but case control studies have linked several risk factors with the disease including age, family history, apolipoprotein (Apo) E4 status, head injury, depression, hypertension, diabetes, high cholesterol, atrial fibrillation, presence of cerebral emboli, and low physical and cognitive activity. Some risk factors are potentially modifiable. Neurotic (or senile) plaques and neurofibrillary tangles are the primary histological features of Alzheimer's disease [7].

Causes [1].

Neuro-chemical factors	Acetylcholine, Somatostatin, Substance P, Norepinephrine.
Environmental factor	Cigarette smoking, Certain Infection, Metals or Industrial toxins.

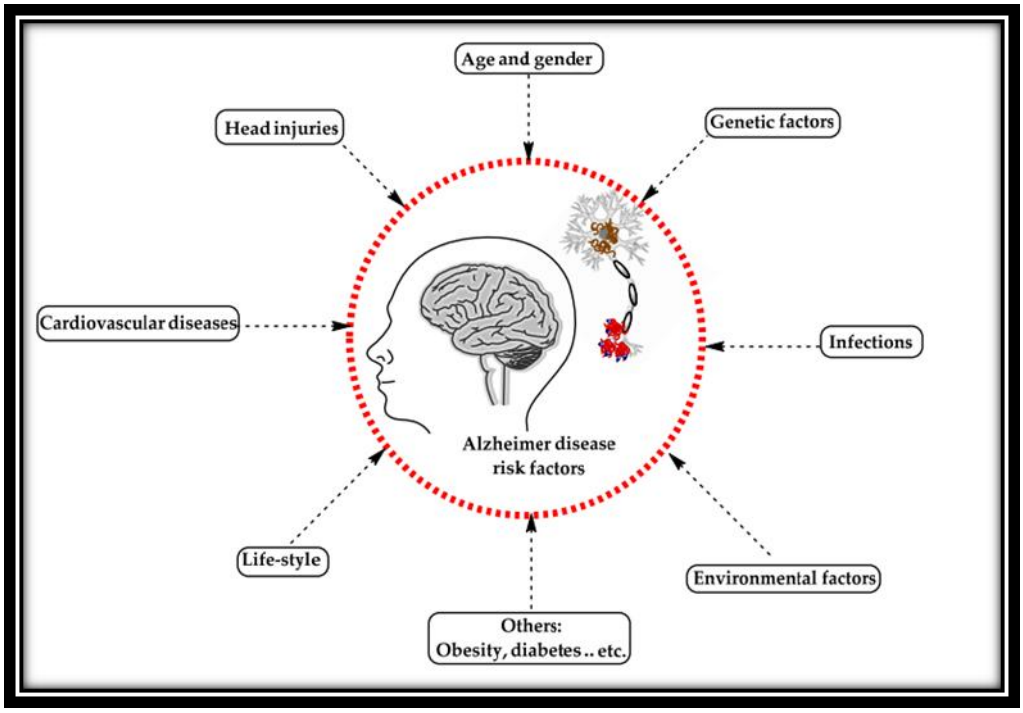

Fig.1 Risk factor of Alzheimer disease

Treatment:

No new drug has been approved by FDA for AD since 2003 and there are no approved DMTs for AD, despite many long and expensive trials. As a matter of fact, more than 200 research projects in the last decade have failed or have been abandoned.10 Nevertheless, drug pipeline for AD is still full of agents with mechanisms of action (MOA) that target either disease modification or symptoms. Some of the recent failures of anti-amyloid agents in phase 3 clinical trials in patients with early-stage, mild, or mild-to-moderate stage AD. The National Institute on Aging and the Alzheimer's Association (NIA-AA) proposed a new framework for research, which requires the application of amyloid, tau, and neurodegeneration biomarkers to clinical trials, succeeds in precise classification of patients in AD stages, and can be used to assist clinical trials design. Tau positron emission tomography (tau PET), neurofilament light, and neurogranin are the new biomarkers that are increasingly used by clinical trials. A search for phases 1, 2, and 3 "recruiting" or "active but not recruiting" clinical trials for AD in clinicaltrials.gov (accessed August 19, 2019) showed 165 outcomes. The last annual review of the drug development pipeline for AD examined clinicaltrials.gov in February, 2019 (132 agents in 156 trials) and provides information and conclusions available at that time: 28 drugs in 42 clinical trials in phase 3 trials, 74 drugs in 83 phase 2 trials, and 30 drugs in 31 phase 1 trials. The tested agents are classified as DMTs (73%), symptomatic cognitive enhancers (13%), and symptomatic for the treatment of BPSDs (11%).4 The DMT agents were further separated into small molecules or biologics (monoclonal antibodies [mAbs] and other immunotherapies) [2].

Currently, Alzheimer's disease cases worldwide are reported to be around 24 million, and in 2050, the total number of people with dementia is estimated to increase 4 times. Even though AD is a public health issue, as of now, there is only two classes of drugs approved to treat AD, including inhibitors to cholinesterase enzyme (naturally derived, synthetic and hybrid analogues) and antagonists to N-methyl d-aspartate (NMDA). Several physiological processes in AD destroy Ach-producing cells which reduce cholinergic transmission through the brain. Acetylcholinesterase inhibitors (AChEIs), which are classified as reversible, irreversible, and pseudo-reversible, act by blocking cholinesterase enzymes (AChE and butyryl cholinesterase (BChE)) from breaking down ACh, which results in increasing ACh levels in the synaptic cleft [95–97]. On the other hand, overactivation of NMDAR leads to increasing levels of influxed Ca2+, which promotes cell death and synaptic dysfunction. NMDAR antagonist prevents overactivation of NMDAR glutamate receptor and hence, Ca2+ influx, and restores its normal activity [3].

Generally, the primary care physician, who is responsible for directing the care, as well as preventing and treating comorbid medical conditions of persons with AD, works in conjunction with professional and nonprofessional health care providers and the far nil.] All persons involved should recognize that treatment and care will be long term and that riot all individuals with AD will be institutionalized [6].

Pharmacological Treatment:

♣ Memantine:

Memantine is approved for the treatment of moderate to severe AD, and has now received a limited recommendation by the UK's National Institute for Clinical Excellence for patients who fail other treatment options. Within the new guidance, memantine is recommended as an option for managing AD for people with: moderate AD who are intolerant of or have a contraindication to AchE (acetyl cholinesterase) inhibitors or those with severe AD.

♣ Donepezil:

Donepezil is indicated for the symptomatic treatment of mild to moderate AD. It is specific and reversible inhibitor of acetyl cholinesterase by increasing the levels of available Ach. Donepezil may compensate for the loss of functioning cholinergic brain cells. Common side-effects include bradycardia, nausea, diarrhoea, anorexia and abdominal pain.

♣ Galantamine:

Galantamine is used for the treatment of mild moderate AD and various other memory impairments particularly those of vascular origin. Galantamine is a competitive and reversible cholinesterase inhibitor. It reduces the action action of AchE and therefore tends to increase the concentration of Acetyl choline in the brain. It is hypothesized that this action might relieve some of the symptoms of Alzheimer's. It is also an allosteric ligand at nicotinic acetyl choline receptor.

♣ Tacrine

It has numerous mechanisms of action. The putative principle mechanism of AD is as a non-competitive reversible Acetyl cholinesterase's inhibitor. Somewhat selective for action in the CNS. But the lesions of Alzheimer's exceed the boundaries of the cholinergic systems to include nor-adrenaline neuro-transmitters decrease vascular perfusion. It may be fortunate that Tacrine has a wide variety of actions. Tacrine blocks Na-K channels. it has direct post synaptic muscarinic activity alters MAO uptake, increase release of 5 HT, NA and Dopamine, inhibit MOA A and B, stimulate cholinergic firing, interacts with N-methyl-D-aspartate phencyclidine receptors.

♣ Rivastigmine:

It is a parasympathomimetic or cholinergic agent for the treatment of mild to moderate dementia of the Alzheimer's type and dementia due to parkinsonism disease. The drug can be administered orally or via a transdermal patch, the later form reduces the prevalence of side effects, [24] which typically include nausea and vomiting [4].

Non-pharmacologic Treatments:

- AD bar ways are divided into 2 teams, the primary related to manner and also the second with diet and chemical compounds.

• Lifestyle: -

Lifestyle ways embody physical activity, mental challenges, energy restriction, and socialization as preventive factors in AD. Physical activity like aerobics was related to the reduction of AD deficits during a cohort study. This wasn't in step with studies that thought of a little range of cases 107. It's been projected that mental challenges could defend against psychological feature decline and doubtless against AD. Pc courses and psycho education have moderate helpful effects. Stimulation by psychological feature activities has been related to a rise in neurotic density that provides brain reserve and physical property physical property. The relation between caloric restriction and brain motivation is very important since a few years past humans required to get their food by killing wild animals and sometimes vigorous exercise was needed.

Diet and Chemical Substances: -

Dietary supplements for bar of AD were studied with vitamins like B6, B12, folates, and E, C, and D vitamins. Vitamin B studies created mixed results; on one hand, a biennial treatment with homocysteine and vitamin B in 271 patients indicated a major distinction compared to placebo in whole brain atrophy, whereas different reports indicate completely different results. It's been projected that vitamin M has neuroprotective activity through associate epigenetic mechanism that inhibits amyloid-β amide accumulation. Studies with 2000 IU of tocopherol didn't indicate a protecting result for AD with 3 years of treatment, nor with the combined treatment with water- soluble vitamin to boot, does ergocalciferol supplementation improve psychological feature performances [8].

Brain imaging Image of brain is used to identify abnormalities related to condition other than AD like strokes, trauma or tumours they cause cognitive changes [1].

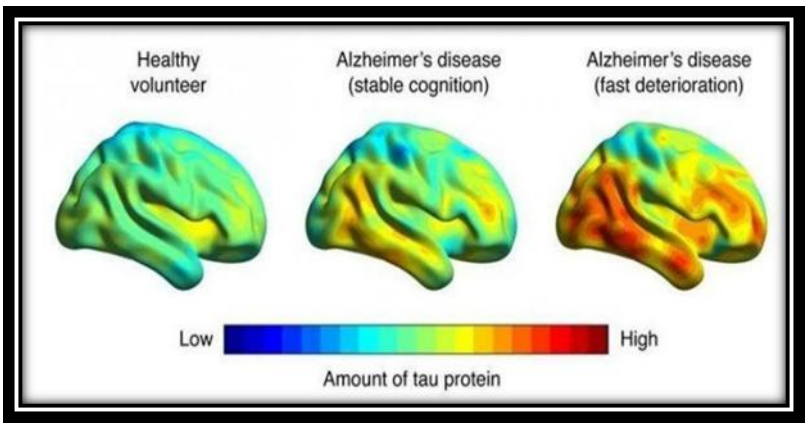

Fig.2 Amount of tau protein in AD

❖ **Current management of AD:**

A multifactorial tailored management of AD is attempted nowadays based in the following components.

1. Open physician, caregiver, and patient communication:

- A sincere and successful conveying of information and feelings between them will offer opportune identifying of symptoms, exact evaluation and diagnosis, and suitable guidance.

2. Behavioral approaches:

- Consistency and simplification of environment
- Established routines
- Communicative strategies such as calm interactions, providing pleasurable activities, using simple language and "saying no" only when safety is concerned
- Timely planning for legal and medical decisions and needs
- Cognitive behavioral therapy
- Exercise therapy, light therapy, music therapy

3. Caregiver support

- Planned short rest periods for the caregiver

- Psychoeducation including preparing for effects of dementia on cognition, function and behaviors, expectations, avoiding situations that can worsen the symptoms or increasing the dangers for safety and well-being
- Encouraging the development of support networks for the caregivers.

4. Pharmacological interventions

FDA-approved AD medications. The AChEIs donepezil, galantamine, rivastigmine, and the NMDA antagonist memantine are the only FDA-approved AD medications.10 AChEIs attempt at reducing the breakdown of acetylcholine levels in the brain of the patients with AD by inhibiting the responsible enzyme acetylcholinesterase in the synaptic cleft.5 Thus, AChEIs enhance central cholinergic neurotransmission and finally tend to mitigate decline in cognition at least during the first year of treatment. Further decline occurs, but even temporary discontinuation of these drugs results in rapid decline and is associated with greater risk of nursing home placement. Medications for BPSD. Antipsychotics and antidepressants remain the main medications for BPSD. Selective serotonin reuptake inhibitors are preferred for treating depression and anxiety. Drugs with low anticholinergic effects and an acceptable tolerability, such as sertraline, citalopram, and escitalopram, are more appropriate. Antipsychotics should be administered only when a significant safety risk for the patient or for the caregivers by aggressive behaviors makes them necessary. Controversial and limited evidence cannot adequately support the use of benzodiazepines, anticonvulsants stimulants, or dextromethorphan/quinidine. Pharmacological approaches to managing BPSD are highly individualized and changeable, depending on patient's comorbidities, stage of the disease, and symptoms, severity [2].

❖ **Pharmacological Approach**

Drugs which are used for dementia and cerebral disorder in Alzheimer Disease The indications of cognition enhancer are as follows:

- Alzheimer Disease or multiple infarct dementia
- Mild cognitive impairment and episodic memory lapses
- Mentally retard children, learning defects, attention deficit disorder or personality disorder
- Sequel of head injury or brain surgery Drugs used for the treatment for Alzheimer disease.

❖ Cholinergic Activators

- Rivastigmine
- Donepezil
- Galantamine
- Tacrine
- Glutamate Antagonists (NMDA)
- Memantine

❖ Miscellaneous Drugs

- Piracetam
- Dihydroergotamine
- Pyritinol
- Citicoline
- Piribedil
- Ginkgo biloba [1].

❖ **New medicines developed in Alzheimer disease**: - [9].

Drug name	**Indication**	**Company**	**Development Status**
ABT-126 acetylcholinesterase inhibitors	Alzheimer disease	Abbott	Phase 2
ABT-126	Alzheimer disease	Abbott	Phase 2
LY2886721	Alzheimer disease	Eli Lilly and Company	Phase 1
AZD3480	Alzheimer disease	Targacept Inc.	Phase 2
AVP-923 (dextromethorphan/quinidine)	Alzheimer disease, mild cognitive impairment	Avanir Pharmaceuticals	Phase 2
MABT5102A	Alzheimer disease	Genentech	Phase 2

AZD5213	Alzheimer disease	AstraZeneca	Phase 2
Gantenerumab	Alzheimer disease	Hoffmann-La Roche	Phase 3
AAB-003 (PF-05236812)	Alzheimer disease	Pfizer	Phase 1
BMS-241027	Alzheimer disease	Bristol-Myers Squibb	Phase 1
MABT5102A	Alzheimer disease	Genentech	Phase 2
BIIB037	Alzheimer disease prodromal or mild AD	Biogen Idec	Phase 1
GSK2647544	Alzheimer disease	GlaxoSmithKline	Phase 1

Potential herbal drugs for AD

There are common traditional Indian plants, which could be used for the treatment of Alzheimer's, dementia and other neurological disorders. Rasayana drugs of Ayurveda are rich in antioxidants and immunomodulatory agents. The strong antioxidant potential of some of these drugs has already been proven. As the majority of diseases are linked to disruption of the delicate balance between oxidants and antioxidants, the ability to scavenge free radicals or to activate oxidant defences of cells can be thought of as their main mechanism of action.

Ashwagandha

It belongs to the Solanaceae family and is a shrub. It is regarded as an adaptogen, a benign drug that normalises physiological processes in response to prolonged stress by activating the immunological and endocrine systems..

Brahmi

Bacopa monniera it belong to family Scrophulariaceae it has been used for thousands of years as a well-respected brain tonic for reviving intelligence, a stress-relieving agent for anxiety, and a way to improve cognitive abilities.

Gotu kola

Centellaasiatica, often known as gotu kola or mandookaparni, is a member of the Umbelliferae (family Apiaceae). It has been used to sharpen focus, improve memory, and increase alertness. It is a psychotropic herb that is used to relieve stress and anxiety.

Chandan

Chandan (Santalum album) belonging to the Santalaceae family. The potential of this plant is to increase memory and cognitive functions (as described in the siddhas).

Bhilawa

Bhilawa (Semencarpusanacardium) belonging to Anacardiaceae family**.** It acts as a brain tonic and is a powerful antioxidant.

Haldi

Haldi (Curcuma longa) is used to treat most chronic diseases**,** including neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune**,** and neoplastic diseases. Curcumin is a therapeutically potential herbal medicine for AD [10].

Conclusion

Alzheimer's disease is a very complicated and stressful disease majorly affect the old age people. There is no cure to this disease and difficult to diagnose. Alzheimer disease is a complex neurodegenerative disease with multifactorial etiology involving multiple neurotransmitter systems. Benefit for the treatment of systems in mild to serve AD using AchEls and Memantine is seen complication in medicine, or medical complication, is an unfavorable result of disease, health condition, or treatment. Also, there is cautious optimism for successful disease modification using number of agents currently under study.

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