



DISEASE PROGRESSION AND TREATMENT STRATEGIES FOR THE MANAGEMENT OF ALZHEIMER'S DISEASE: AN OVERVIEW

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ABSTRACT

Alzheimer's is a disease which pathologically involves production of β -amyloid peptide ($A\beta$). Beta-amyloid initially occurs as small soluble clusters which can travel freely in the brain, then finally occurs as plaques which is associated with Alzheimer's. Extracellular depositions of $A\beta$ along with amyloid precursor protein (APP) are the major pathological process of Alzheimer's disease. Our discovery suggests that Alzheimer's disease starts to manifest long before plaque formation. The study showed that in this clustered form; beta-amyloid can bind strongly to a receptor on nerve cells, setting in motion an intercellular process that erodes their synapses with other nerve cells with disease progression in the living patient. The current therapeutic efforts are directed towards developing the review to explore the targeted effective therapeutic potential for the treatment of Alzheimer's disease which may alter the course or progression of the underlying disease by preventing the formation or clearing of plaques (beta-amyloid) fragments from the brain of the patients. The report summarizes information concerning the all aspects of cellular activities and disease progression of Alzheimer's disease in order to provide sufficient baseline information that could be used in drug discovery campaigns and development process, thereby providing new functional leads for Alzheimer's disease.

KEYWORDS: Alzheimer's disease, beta-amyloid, amyloid precursor protein, plaques.

INTRODUCTION

Alzheimer's disease is 4th leading disease in the world. About 4 million of Americans 90 percentages of peoples are in the age of 65 and older is suffering from Alzheimer's disease.^[1] The prevalence of Alzheimer's disease doubles for every five years beyond age of sixty five.^[2]

Alzheimer's disease is an irreversible, progressive brain disorder related to changes in nerve cells that result in the death of brain cells. Dementia is a loss of neuron population which cause confusion, irritability, aggression, mood swings, language breakdown and long-term memory loss.^[3, 4] In most people with Alzheimer's, symptoms first appear after the age of sixty.

Alzheimer's disease (AD) pathogenesis is widely believed to be driven by the production and deposition of the β -amyloid peptide ($A\beta$). It is caused by the development of two kinds of microscopic alterations in the brain known as 'plaques' and 'tangles'.^[5] Plaques are formed due to the accumulation of the abnormal protein beta-amyloid between neurons. Neurofibrillary tangles composed of the insoluble tau protein at cortex region further spread to hippocampus, which is essential in forming memories.

Beta-amyloid begins life as a solitary molecule but tends to bunch up — initially into small clusters that are still soluble and can travel freely in the brain, and finally into the plaques that are hallmarks of Alzheimer's. Abnormal processing and extracellular deposition of $A\beta$, a proteolytic derivative of the larger amyloid precursor protein (APP) is a key step in the pathogenesis of Alzheimer's disease.^[6]

The efforts has been made to explore all aspects of cellular activities and disease progression of Alzheimer's disease in order to provide base for developing therapeutic potential interaction and inhibit amyloid peptide deposition in brain.

Biochemical Characteristics of Alzheimer's

Brain is a part of the central nervous system that is located within the skull of vertebrates, functioning as the coordinating centre of sensation, intellectual and distributor of information for the body. Neuron is a structural and functional unit of brain. Degeneration of Neurons leads to disorders, such as Parkinson's disease, multiple sclerosis, and Alzheimer's disease. Alzheimer's disease is a progressive, incurable, degenerative disease of brain was first described by German psychiatrist Alois Alzheimer in 1906 and was named after him Berchtold

NC and Cotman CW 1998.^[7] Alzheimer's disease (AD) is characterized by chronic, progressive neurodegeneration. The precise aetiology of AD is still not fully clarified but is known to be complex and multifactorial, with a notable overlap between familial and non-familial forms but also with different forms of dementia such as vascular dementia. The neurodegeneration seen in fig.-1 in which AD involves early synaptotoxicity and loss of neurophil, neurotransmitter disturbances, accumulation of extracellular β -amyloid ($A\beta$).

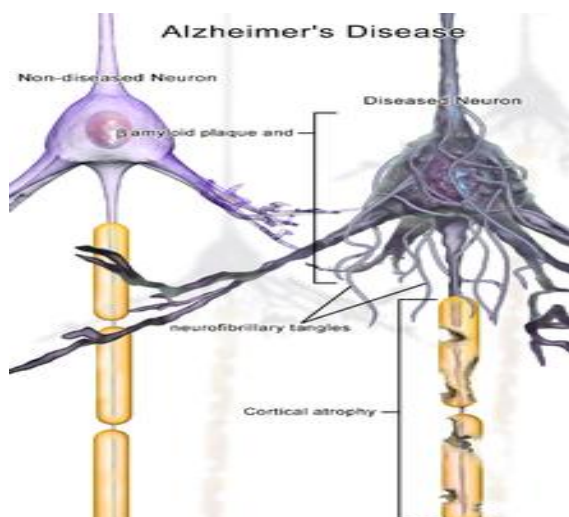


Fig. 1: Neuronal degeneration associated with Alzheimer's disease

deposits (amyloid/senile plaques) and intracellular neurofibrils (neurofibrillary tangles, NFTs), gliosis and only at later stages overt loss of neurons and associated brain atrophy.^[8-11] At early stages of the disease, the entorhinal cortex and hippocampus are particularly affected, and this is associated with deficits in cognition/memory.^[12] Over the course of AD, up to 80% of neurons in the hippocampus die and the progressive symptoms of AD manifest themselves as cognitive disturbances, reduced ability to cope with everyday life and worsening of clinical global impression score.^[13]

Cell Signalling

Cell Signalling Signals that form memories and thoughts move through an individual nerve cell as a tiny electrical charge. Nerve cells connect to one another at synapses. When a charge reaches a synapse, it may trigger release of tiny bursts of chemicals called neurotransmitters. The neurotransmitters travel across the synapse, carrying signals to other cells.^[14]

Scientists have identified dozens of neurotransmitters.

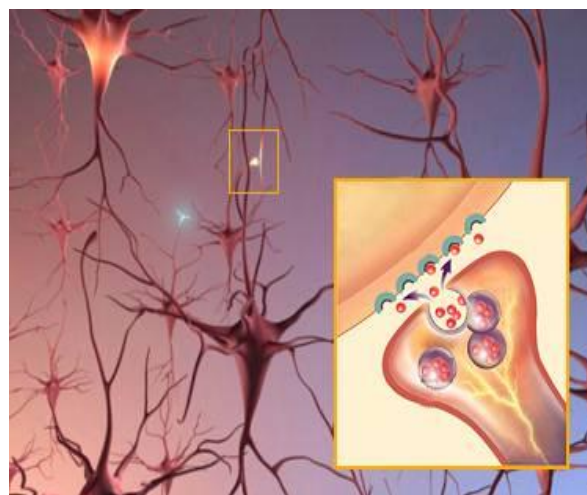


Fig. 2: Cell Signalling

Alzheimer's disease disrupts both the way electrical charges travel within cells and the activity of neurotransmitter as shown in fig. 2.

Plaques

Beta-amyloid is chemically "sticky" and gradually builds up into plaques as shown in fig 3. Plaques form when protein pieces called beta-amyloid (BAY-tuh AM-uh-loyd) clump together and from a larger protein found in the fatty membrane surrounding nerve cells.

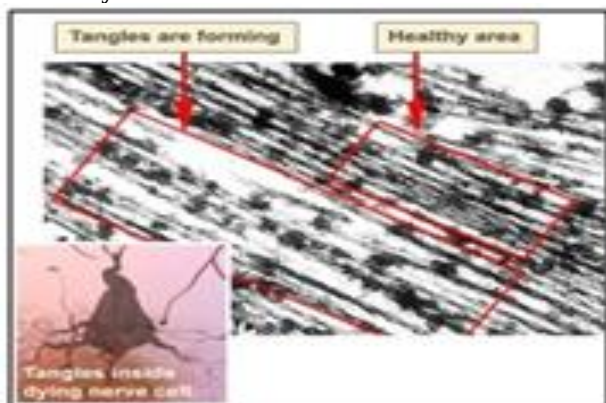


Fig. 3: Plaques

The most damaging form of beta-amyloid may be groups of a few pieces rather than the plaques themselves. The small clumps may block cell-to-cell signalling at synapses. They may also activate immune system cells that trigger inflammation and devour disabled cells.^[15-16]

Tangles

Tangles destroy a vital cell transport system made of proteins. These electron microscopes picture in fig. 4 shows a cell with some healthy areas and other areas where tangles are forming.

In healthy areas**Fig. 4: Tangles**

The transport system is organized in orderly parallel strands somewhat like railroad tracks. Food molecules, cell parts and other key materials travel along the "tracks. A protein called tau (rhymes with wow) helps the tracks stay straight.^[17]

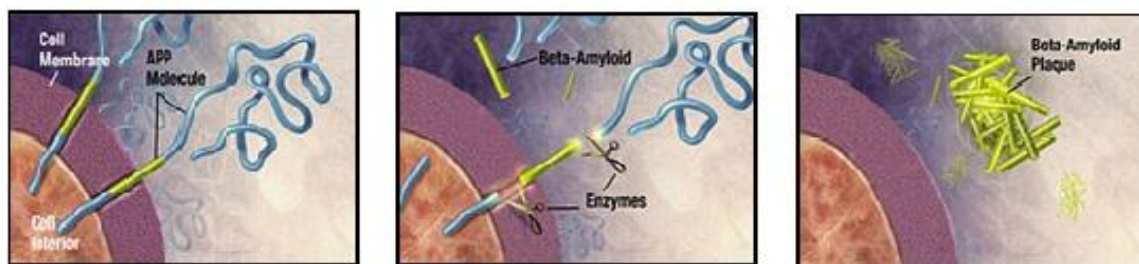
In areas where tangles are forming:

- Tau collapses into twisted strands called tangles.
- The tracks can no longer stay straight. They fall apart and disintegrate.

Beta amyloid

Alzheimer's disease (AD) is characterized due to the presence of senile plaques and tangles. The plaques are made up of beta-amyloid protein. Beta-Amyloid (beta A) is normally produced as a nontoxic soluble peptide. In Alzheimer disease, beta A aggregates and accumulates in the brain as inert diffuse plaques or compact plaques associated with neurodegenerative changes.

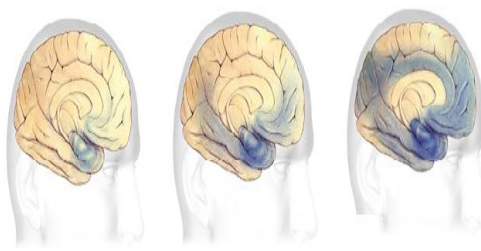
Amyloid beta monomers are soluble and contain short regions of beta sheet and polyproline II helix secondary structures in solution, though they are largely alpha helical in membranes;^[18] however, at sufficiently high concentration, they undergo a dramatic conformational change to form a beta sheet-rich tertiary structure that aggregates to form amyloid fibrils. These fibrils deposit outside neurons in dense formations known as senile plaques or neuritic plaques, in less dense aggregates as *diffuse plaques*, and sometimes in the walls of small blood vessels in the brain in a process called amyloid angiopathy.

**Fig. :5 Conformational Changes of Beta amyloid in AD**

Amyloids are aggregates of proteins that become folded into a shape that allows many copies of that protein to stick together. In the human body, amyloids are usually unhealthy developments, as these previously healthy proteins most often lose their normal physiological function and form large fibrils. These fibrils disrupt the healthy function of nearby tissues and organs. Such amyloids have been known to arise from at least 18 different proteins and polypeptides, and have been associated with more than 20 human diseases, known as amyloidosis, and may play a role in some neurodegenerative disorders.^[19]

In AD patients, learning and memory are impaired following loss of the cholinergic marker enzyme, choline acetyltransferase (ChAT). Nabeshima T *et al.*, (1994) investigated whether memory impairment were produced after 2 weeks continuous infusion of beta-amyloid protein (3, 30 and 300 pmol/day) into the cerebral ventricles in adult Albino wistar rats. Water maze and passive avoidance tasks were carried out to determine the

ability of learning and memory in beta-amyloid protein-treated rats. The performance was impaired in both tasks of beta-amyloid protein-treated rats. ChAT activity in the hippocampus (300 pmol/day) and frontal cortex (3 and 30 pmol/day) significantly decreased. These results suggest that beta-amyloid protein treated rats produce neurodegeneration and impairment of learning and memory and it could be used as an animal model for AD.^[20]

**Fig. 6: Stages of Alzheimer's (Overview of disease progression in brain)**

Overview of disease progression

Changes in the brain related to Alzheimer's begin years before any signs of the disease. This time period, which can last for years, is referred to as preclinical Alzheimer's disease. The stages below provide an overall idea of how abilities change once symptoms appear and should only be used as a general guide.

They are separated into three different categories: mild Alzheimer's disease, moderate Alzheimer's disease and severe Alzheimer's disease. Be aware that it may be difficult to place a person with Alzheimer's in a specific stage as stages may overlap. Plaques and tangles (shown in the blue-shaded areas) tend to spread through the cortex in a predictable pattern as Alzheimer's disease progresses.^[21]

The rate of progression varies greatly. People with Alzheimer's live an average of eight years, but some people may survive up to 20 years. The course of the disease depends in part on age at diagnosis and whether a person has other health conditions.

- **Earliest Alzheimer's** - changes may begin 20 years or more before diagnosis.
- **Mild to moderate Alzheimer's stages** - generally last from 2 - 10 years.
- **Severe Alzheimer's** - may last from 1 - 5 years.

Mild Alzheimer's disease / Earliest stage of Alzheimer's

In the early stages of Alzheimer's, a person may function independently. He or she may still drive, work and be part of social activities. Despite this, the person may feel as if he or she is having memory lapses, such as forgetting familiar words or the location of everyday objects.^[22]

- Problems coming up with the right word or name
- Trouble remembering names when introduced to new people
- Having greater difficulty performing tasks in social or work settings
- Forgetting material that one has just read
- Losing or misplacing a valuable object
- Increasing trouble with planning or organizing

In the earliest stages, before symptoms can be detected with current tests, plaques and tangles begin to form in brain areas involved in:

- Learning and memory
- Nutrients and other essential supplies can no longer
- Move through the cells, which eventually die.
- Thinking and planning.

Mild to moderate Alzheimer's

In mild to moderate stages, brain regions important in memory and thinking and planning develop more plaques and tangles than were present in early stages. As a result it, individuals develop problems with memory or

thinking serious enough to interfere with work or social life. They may also get confused and have trouble handling money, expressing them and organizing their thoughts. Many people with Alzheimer's are first diagnosed in these stages.^[23]

Plaques and tangles also spread to areas involved in:

- Speaking and understanding speech

Moderate Alzheimer's disease (middle-stage)

- Forgetfulness of events or about one's own personal history
- Feeling moody or withdrawn, especially in socially or mentally challenging situations
- Being unable to recall their own address or telephone number or the high school or college from which they graduated
- Confusion about where they are or what day it is
- The need for help choosing proper clothing for the season or the occasion
- Trouble controlling bladder and bowels in some individuals
- Changes in sleep patterns, such as sleeping during the day and becoming restless at
- Severe Alzheimer's disease (late-stage)

In the final stage of this disease, individuals lose the ability to respond to their environment, to carry on a conversation and, eventually, to control movement. They may still say words or phrases, but communicating pain becomes difficult. As memory and cognitive skills continue to worsen, personality changes may take place and individuals need extensive help with daily activities.^[24]

- Require full-time, around-the-clock assistance with daily personal care
- Lose awareness of recent experiences as well as of their surroundings
- Require high levels of assistance with daily activities and personal care
- Experience changes in physical abilities, including the ability to walk, sit and eventually, swallow
- Have increasing difficulty communicating
- Become vulnerable to infections, especially pneumonia.

Severe Alzheimer disease

In advanced Alzheimer's disease, most of the cortex is seriously damaged. The brain shrinks dramatically due to widespread cell death. Individuals lose their ability to communicate, to recognize family and loved ones and to care for themselves.^[25]

Alzheimer's changes the whole brain

Alzheimer's disease Guide overview & facts our brain is your most powerful organ, yet weighs only about three pounds. It has a texture similar to firm jelly.^[26]

It has three main parts:

1. The cerebrum fills up most of your skull. It is involved in remembering, problem solving, thinking and feeling. It also controls movement.
2. The cerebellum sits at the back of your head, under the cerebrum. It controls coordination and balance.
3. The brain stem sits beneath your cerebrum in front of your cerebellum. It connects the brain to the spinal cord and controls automatic functions such as breathing, digestion, heart rate.

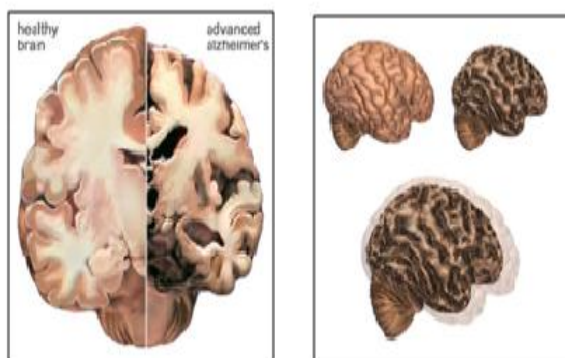


Fig. :7 Alzheimer's changes the whole Brain

Alzheimer's disease leads to nerve cell death and tissue loss throughout the brain. Over time the brain shrinks dramatically affecting nearly all its function.^[27-28]

These images show

- A brain without the disease.
- A brain with advanced Alzheimer's.
- How the two brains compare.

In the Alzheimer's brain the cortex shrivels up damaging areas involved in thinking. Planning and remembering.

- Shrinkage is especially severe in hippocampus an area of the cortex that plays a key role in formation of new memories.
- Ventricles (fluid-filled spaces within the brain) grow brain.

Neuropathology

At a macroscopic level, AD is characterized by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe and parts of the frontal cortex and cingulate gyrus.^[29] Both amyloid plaques and neurofibrillary tangles are clearly visible by microscopy in AD brains.^[30]

Plaques are dense, mostly insoluble deposits of protein and cellular material outside and around neurons. The brains of AD patients have them to a much greater extent and in different brain locations.

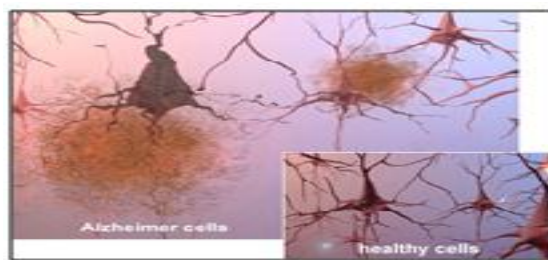


Fig. :8 Healthy & Alzheimer cell

Alzheimer's and Dementia Diagnosis Testing for Earlier Diagnosis

What if we could diagnose Alzheimer's before symptoms started? The hope is, future treatments could then target the disease in its earliest stages, before irreversible brain damage or mental decline has occurred. Research on new strategies for earlier diagnosis is among the most active areas in Alzheimer's science, and funding from the Alzheimer's Association has spurred significant advances and steady progress.^[31]

Biomarkers for earlier detection

Current diagnosis of Alzheimer's relies largely on documenting mental decline. We now know that Alzheimer's has already caused severe brain damage in individuals who are diagnosed in this way. Researchers hope to discover an easy and accurate way to detect Alzheimer's before these devastating symptoms begin. Experts believe that biomarkers (short for "biological markers") offer one of the most promising paths. A biomarker is something that can be measured to accurately and reliably indicate the presence of disease. An example of a biomarker is fasting blood glucose (blood sugar) level, which indicates the presence of diabetes if it is 126 mg/dL or higher.^[32]

• Brain Imaging/ neuroimaging

Neuroimaging is among the most promising areas of research focused on early detection. Today, a standard workup for Alzheimer's disease often includes structural imaging with magnetic resonance imaging (MRI) or computed tomography (CT). These tests are currently used chiefly to rule out other conditions that may cause symptoms similar to Alzheimer's but require different treatment. Structural imaging can reveal tumours, evidence of small or large strokes and damage from severe head trauma or a build up of fluid in the brain.^[33]

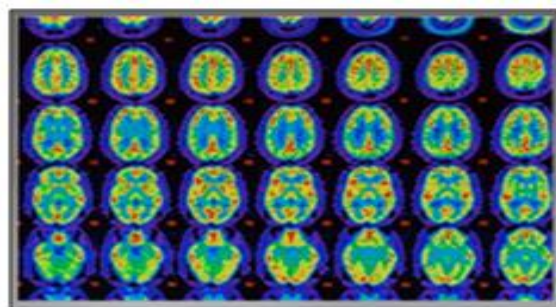


Fig. :9 Diagnosis test of Alzheimer

- **Structural imaging** studies have shown that the brains of people with Alzheimer's shrink significantly as the disease progresses. Research has also shown that shrinkage in specific brain regions such as the hippocampus may be an early sign of Alzheimer's. However, scientists have not yet agreed upon standardized values for brain volume that would establish the significance of a specific amount of shrinkage for any individual person at a single point in time.^[34]
- **Functional imaging** research with positron emission tomography (PET) and other methods suggests that those with Alzheimer's typically have reduced brain cell activity in certain regions. For example, studies with fluorodeoxyglucose (FDG)-PET indicate that Alzheimer's disease is often associated with reduced use of glucose (sugar) in brain areas important in memory, learning and problem solving. However, as with the shrinkage detected by structural imaging, there is not yet enough information to translate these general patterns of reduced activity into diagnostic information about individuals.^[35]
- **Molecular imaging technologies** are among the most active areas of research aimed at finding new approaches to diagnose Alzheimer's in its earliest stages. Molecular strategies may detect biological clues indicating Alzheimer's is under way before the disease changes the brain's structure or function, or takes an irreversible toll on memory, thinking and reasoning. Molecular imaging also may offer a new strategy to monitor disease progression and assess the effectiveness of next-generation, disease-modifying treatments. Several molecular imaging compounds are being studied and two have now been approved for clinical use.^[36]
- **Pittsburgh compound B (PIB)** was the first radiotracer capable of highlighting deposits of beta-amyloid-one pathological hallmark of Alzheimer's disease—in living individuals during a PET scan. The Alzheimer's Association helped fund early PIB development. The original phase of the ADNI project has now been completed, but the Alzheimer's Association has supported two follow-up study phases, known as ADNI-GO and ADNI-2. These studies are continuing research into the uses of brain imaging for detecting and monitoring Alzheimer's disease in its earliest stages.^[37]
- A cerebrospinal fluid (CSF) protein CSF is a clear fluid that bathes and cushions the brain and spinal cord. Adults have about 1 pint of CSF, which physicians can sample through a minimally invasive procedure called a lumbar puncture, or spinal tap. Research suggests that Alzheimer's disease in early stages may cause changes in CSF levels of tau and

beta-amyloid, two proteins that form abnormal brain deposits strongly linked to the disease.^[38]

• **Mild cognitive impairment (MCI)**

Research has shown that individuals with mild cognitive impairment (MCI) have a significantly increased risk of developing Alzheimer's disease within a few years, compared to people with normal cognitive function; research surrounding MCI offers another potential path to earlier diagnosis.^[39]

Symptoms

Alzheimer's is a type of dementia that problems with memory, thinking and behaviour. Symptoms usually develop slowly and get worse over time, becoming severe enough to interfere with daily tasks.^[40]

Common Symptoms are enlisted below.

- 1) Memory loss
- 2) Trouble planning and problem solving
- 3) Daily tasks are a challenge
- 4) Times and places are confusing
- 5) Changes in vision
- 6) Words and conversations are frustrating
- 7) You lose things
- 8) Lapse in judgment
- 9) Social withdrawal
- 10) Mood changes

Treatments Strategies for the management of Alzheimer's

Alzheimer's disease (AD) has a complex pathology with multifactorial mental illness, characterized by loss of memory and cognition. The etiological factors include oxidative stress, inflammation, A β over expression, tau hyper-phosphorylation, metal toxicity etc.

To understand how Alzheimer's medications work, first need to understand the communication network in the brain. The picture below depicts nerve cells, or neurons, in the brain. Neurons are the chief cells destroyed by Alzheimer's disease.

In the brain, neurons connect and communicate at synapses, where tiny bursts of chemicals called neurotransmitters carry information from one cell to another. Alzheimer's disrupts this process, and eventually destroys synapses and kills neurons, damaging the brain's communication network.^[41]

Current FDA-approved Alzheimer's drugs support this communication process through two different mechanisms.

- 1) Cholinesterase inhibitors work by slowing down the process that breaks down a key neurotransmitter. Donepezil, galantamine and rivastigmine are cholinesterase inhibitors.

2) Memantine, the fifth Alzheimer's drug, is an NMDA (N-methyl-D-aspartate) receptor antagonist, which works by regulating the activity of glutamate, an important neurotransmitter in the brain involved in learning and memory. Attachment of glutamate to cell surface "docking sites" called NMDA receptors permits calcium to enter the cell. This process is important for cell signalling, as well as learning and memory. In Alzheimer's disease, however, excess glutamate can be released from damaged cells, leading to chronic overexposure to calcium, which can speed up cell damage. *Meantime* helps prevent this destructive chain of events by partially blocking the NMDA receptors. The effectiveness of cholinesterase inhibitors and memantine varies across the population.^[42]

Types of drugs

The U.S. Food and Drug Administration (FDA) has approved two types of medications- cholinesterase inhibitors (Aricept, Exelon, Razadyne) and memantine (Namenda) — to treat the cognitive symptoms (memory loss, confusion and problems with thinking and reasoning) of Alzheimer's disease. There is also a medication that combines one of the cholinesterase inhibitors (donepezil) with memantine called Namzaric.^[43]

As Alzheimer's progresses, brain cells die and connections among cells are lost, causing cognitive symptoms to worsen. While current medications cannot stop the damage Alzheimer's causes to brain cells, they may help lessen or stabilize symptoms for a limited time by affecting certain chemicals involved in carrying messages among the brain's nerve cells. Doctors sometimes prescribe both types of medications together.^[44]

Medications for early to moderate stages

All of the prescription medications currently approved to treat Alzheimer's symptoms in early to moderate stages are from a class of drugs called cholinesterase inhibitors. Cholinesterase inhibitors are prescribed to treat symptoms related to memory, thinking, language, judgment and other thought processes.

Cholinesterase inhibitors

- Prevent the breakdown of acetylcholine (a-SEA-til-KOH-lean), a chemical messenger important for learning and memory. This supports communication among nerve cells by keeping acetylcholine levels high.
- Delay or slow worsening of symptoms. Effectiveness varies from person to person.
- Are generally well tolerated. If side effects occur, they commonly include nausea, vomiting, loss of appetite and increased frequency of bowel movements.

Three cholinesterase inhibitors are commonly prescribed:

- Donepezil (Aricept) is approved to treat all stages of Alzheimer's.
- Rivastigmine (Exelon) is approved to treat mild to moderate Alzheimer's.
- Galantamine (Razadyne) is approved to treat mild to moderate Alzheimer's.

Medication for moderate to severe stages

A second type of medication, memantine (Namenda) is approved by the FDA for treatment of moderate to severe Alzheimer's.^[45]

Memantine is prescribed to improve memory, attention, reason, language and the ability to perform simple tasks. It can be used alone or with other Alzheimer's disease treatments. There is some evidence that individuals with moderate to severe Alzheimer's who are taking a cholinesterase inhibitor might benefit by also taking memantine.

Memantine

- Regulates the activity of glutamate, a chemical involved in information processing, storage and retrieval.
- Improves mental function and ability to perform daily activities for some people.
- Can cause side effects, including headache, constipation, confusion and dizziness.

Table: 1-List of Medication for the Management of Alzheimer's^[46]

Generic	Brand	Approved For	Side effects
Donepezil	Aricept	All stages	Nausea, vomiting, loss of appetite and increased frequency of bowel movements.
Galantamine	Razadyne	Mild to moderate	Nausea, vomiting, loss of appetite and increased frequency of bowel movements.
Memantine	Namenda	Moderate to severe	Headache, constipation, confusion and dizziness.
Rivastigmine	Exelon	Mild to moderate	Nausea, vomiting, loss of appetite and increased frequency of bowel movements.
Memantine + Donepezil	Namzaric	Moderate to severe	Headache, diarrhea, dizziness, loss of appetite, vomiting, nausea, and bruising.

Development of a Transdermal treatment for Alzheimer's Disease

Currently, there are three cholinesterase inhibitors widely used to treat AD patients: rivastigmine, donepezil and galantamine. Rivastigmine provides sustained inhibition of AChE and BuChE, while donepezil and galantamine are selective AChE inhibitors. In 2005, rivastigmine became the first approved treatment for mild to moderate Parkinson's disease dementia (PDD). All cholinesterase inhibitors have been available in oral formulations.

Cholinesterase inhibitors have been shown to exhibit dose-response relationships with higher plasma levels of the drug corresponding to higher levels of enzyme inhibition. However, the incidence of adverse events (AEs) also increases with higher oral doses, particularly gastrointestinal occurrences such as nausea and vomiting.^[47-48] Consequently, not all patients in clinical practice are able to achieve and maintain the recommended therapeutic doses of conventional oral cholinesterase inhibitors.^[49]

Cholinergic side effects are thought to be the result of high peak plasma concentrations of the drug (C_{max}), rapid absorption into the bloodstream resulting in a short time to C_{max} (t_{max}), and the frequency and magnitude of the resulting fluctuations in drug plasma level.^[10] A transdermal patch can provide smooth and continuous delivery of the drug, reducing C_{max} and prolonging t_{max} while maintaining drug exposure.^[50] This pharmacokinetic profile has the potential to reduce the incidence of cholinergic side effects, allowing patients easier access to optimum therapeutic doses, thus improving the effectiveness of treatment over oral administration. Additional benefits of transdermal administration, including a simplified treatment regimen, convenience and ease of use, are discussed by Bernabei and Martinez.^[51]

Recently, first transdermal application system for cholinesterase inhibitors, a rivastigmine transdermal patch has been developed, and is approved in many countries worldwide (including the US, Latin America, Europe and Asia) for the treatment of AD. The rivastigmine patch has also been approved for the treatment of PDD in the US, Latin America and Asia. Rivastigmine is chemically well-suited to transdermal delivery.^[52] As a small (<500Da) lipophilic and hydrophilic molecule, it passes rapidly through the skin and into the bloodstream and is therefore considered a viable patch medication. Moreover, rivastigmine is a potent cholinesterase inhibitor, requiring only small doses of the drug for effective treatment. This enables the patches to be small and discreet, thereby improving adhesion and reducing the risk of frequent adverse skin reactions.^[53]

A transdermal drug delivery system has the potential to change the treatment paradigm for many AD patients.

Alternative & Natural Treatments

Alzheimer's disease is not a normal part of aging, although it's impacting a growing number of adults. Currently incurable, the disease characterized by toxic plaques and tangles in the brain leads to symptoms of memory loss, personality changes, trouble performing everyday tasks and death. Scientists have struggled to bring meaningful therapies to the table, but 2016 marks a year of promising findings, including science-backed evidence that food and exercise plays a huge role in prevention.

Researchers used PET scans to show a Mediterranean diet, regular physical activity and a healthy BMI go a long way in lower your risk of developing the toxic plaques and tangles that lead to Alzheimer's disease.^[54-55]

In other Alzheimer's breakthroughs, researchers have found a link between the gut and Alzheimer's and between certain popular drugs and the disease. A growing number of natural treatments and preventatives may include herbal remedies, marijuana, certain medicinal foods and dietary supplements-showing promise in reversing Alzheimer's related inflammation and memory loss. Claims about the safety and effectiveness of these products, however, are based largely on testimonials, tradition and a rather small body of scientific research.

Alzheimer's Food Diets

Food to Eat

Organic, unprocessed foods: Vegetables, clean meats and fruit.

Antioxidants such as vitamins A, C, E: Antioxidant foods help combat the damage caused by free radicals. Colorful fruits and vegetables are high in antioxidants and should be consumed at every meal.

Omega-3 fats: DHA specifically, which are critical for brain health.

Foods high in zinc — Pumpkin seeds, grass-fed beef and dark chocolate.

Coconut oil- Providing the brain with ketones, which serves as brain fuel instead of glucose. Some people have seen significant improvement to memory after adding coconut to their diet.

Foods to Avoid

Any food containing toxins or additives

These foods can possibly be neurotoxic. Be sure to especially avoid the "dirty dozen": nonorganic fruits and vegetables that are coated with neurotoxic agricultural chemicals. Studies show people with higher levels of organochlorine pesticides in their blood, including DDE, a breakdown compound of DDT, face a higher risk of Alzheimer's disease.^[56]

It's also best to avoid any processed foods.

Alcohol

Alcohol is a toxin and can cause brain cells to die faster than normal. In fact, there is such a thing as “alcohol-related dementia.” Research shows that the frontal lobes of people diagnosed with alcoholism appear particularly susceptible to damage, with evidence of markedly decreased neuron density, volume shrinkage and altered glucose metabolism and perfusion.^[57-58]

Tap water

Tap water may contain environmental toxins, including aluminum salts (see below), so be sure test your water if you drink tap water (or get a recent water testing report if you drink municipal water) and filter out contaminants. Environmental Working Group issued a great drinking water filter to help you find the best one for your circumstance.

Sugar and refined grains

Alzheimer's may be caused by insulin resistance, similar to diabetes. Therefore, keeping your insulin low by eliminating sugar and refined grains will be an important component in maintaining brain health.

Foods packaged in aluminum containers

Aluminum is neurotoxic at high levels, so it's best to avoid it. In fact, research shows aluminum enters neurons similarly to how iron does, leading to aluminum accumulation and neurofibrillary damage linked to Alzheimer's progression.^[59] You should particularly avoid heating food in aluminum; the heat is known to release more toxic compounds.

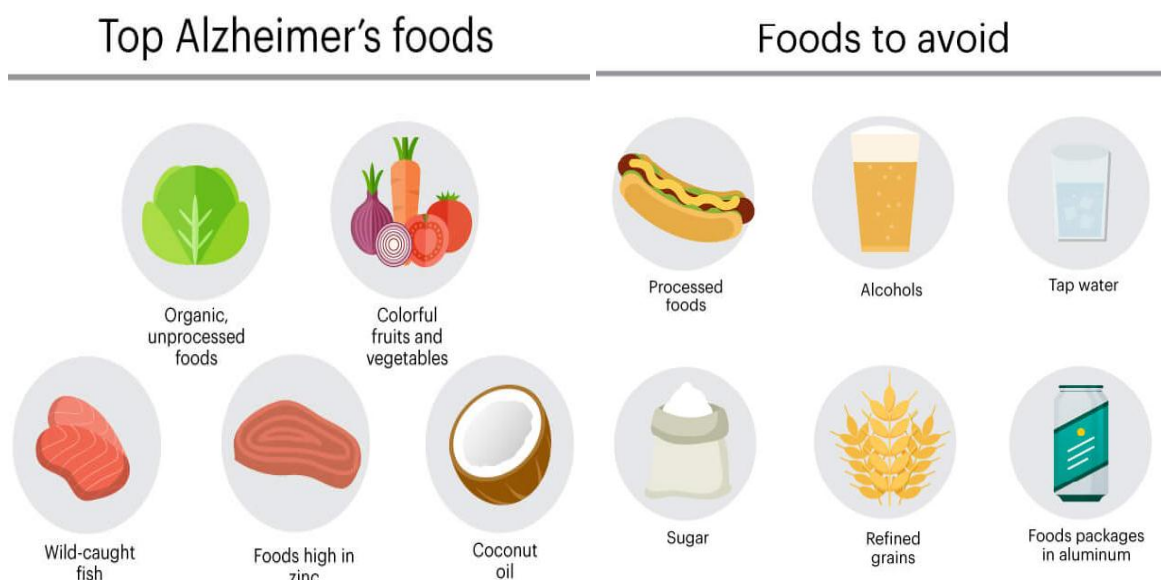


Fig. 10: Food consideration for Alzheimer's disease.

Natural Supplements

Along with diet, these alzheimer's remedies are as part of natural treatment protocol.

1. Fish Oil with DHA (1,000 mg daily)

The fish benefits include DHA, a fatty acid critical for brain function. High-quality fish oil also reduces inflammation.

2. Vitamin D3 (5,000 IU daily)

Vitamin D deficiency could be a risk factor for Alzheimer's. Research shows that ample levels of vitamin D can help prevent tangles and plaques from forming on the brain.^[60]

3. CoQ10 (200 mg daily)

Levels of CoQ10 decrease as we age and some research has shown that supplementation may slow down the progress of Alzheimer's disease.

4. Ginkgo Biloba (120 mg daily)

Ginkgo biloba helps improve brain circulation and memory and can be an effective Alzheimer's natural treatment.

5. Phosphatidylserine (300 mg daily)

Phosphatidylserine improves brain cell communication and memory, and it's shown to be beneficial for early-stage Alzheimer's disease.

Bonus Remedy: Astaxanthin, a carotenoid antioxidant found in wild-caught salmon, can support brain health. Take 2–4 g 2 xs daily.

Essential Oils for Alzheimer's

Frankincense oil and rosemary oil support brain function and neurological development. Put 2 drops of frankincense oil on the roof of your mouth twice daily and rub rosemary oil into scalp after getting out of shower daily.^[61]

Herbal Remedies

Many plants are now being investigated and short listed in Table-2 with inputs from literature and traditional Indian medicinal plants originally classified as brain boosters and as a potential source of new therapy for AD.^[62-63]

Table: 2 List of Indian Medicinal Plants Used as a Brain Boosters

Plant Species & Family	Common Name	Part Used	Active Component	Therapeutic Values
<i>Bacopa monneria</i> Scrophulariaceae	Brahmi	Whole plant	Bacosides	Anti-anxiety activity, anti-fatigue and memory enhancing effects, decreases stress induced biomarkers in hippocampus
<i>Celastrus peniculatus</i> Celastraceae	Malkangani, Intellect Tree	Seeds & Leaves	Celapagine	used to both sharpen mental focus and relax the nerves, brain tonic. ^[64]
<i>Ginkgo biloba</i> Ginkgoaceae	Abricot	Leaves	Ginkgolides	Reduce memory loss, enhance the brain activity and to slow down the degenerative effects of Alzheimer's disease. To improve the symptoms and slow the progression of Alzheimer's disease (AD).
<i>Huperzia serrata</i> Lycopodiaceae	Toothed Clubmoss, Firmoss	Herbs	Huperzine Huperzine A	Antioxidant and neuroprotective properties. Contain acetylcholinesterase inhibitor huperzine A and to improve memory and mental impairment. ^[65]
<i>Ricinus communis</i> Euphorbiaceae	Castor, Errand, Arandi	Seeds	Ricinine	Memory enhancing property
<i>Centella asiatica</i> Apiaceae	Gotukola	Whole plant	Asiaticoside	Memory enhancer
<i>Cannabis sativa</i> Cannabaceae	Marijuana, Hemp, Cannabis	Herbs	Cannabidiol	Anti-oxidant, anti-psychotic, anxiolytic and neuroprotection against A β and hyperphosphorylated tau induced insults in neuronal cells.
<i>Curcuma longa</i> Zingiberaceae	Haldi	Rhizome	Curcumin	Anti-oxidant, anti-inflammatory, neuroprotection against A β
<i>Magnolia officinalis</i> Magnoliaceae	Magnolia	Bark	Magnolol	Neuroprotective against A β toxicity in vitro, prevents cholinergic deficits. ^[66]
<i>Vinca minor or Catharanthus roseus</i> Apocynaceae	periwinkle	Herbs	Vincamine, Vinpocetine	Improves memory in animal models of AD
<i>Physostigma venenosum</i> Leguminosae	Calabar bean	Seeds	Physostigmine	Improves cognition <i>in vivo</i>
<i>Withania somnifera</i> Solanaceae	Ashwagandha	Root	Withanosides	Promotes cognition and memory
<i>Convolvulus pluricaulis</i> , Convolvulaceae	Shankhapushpi	Whole plant	Shankhapushpine	Brightens the memory and intellect. ^[67]
<i>Galanthus Caucasicus</i> Liliaceae	Snowdrop	Bulbs and Flowers	Galantamine	Treatment of mild to moderate Alzheimer's disease and other memory impairments. Selective acetyl-cholinesterase (AChE) Inhibitor. Improve the symptoms of Alzheimer's disease and other form of dementia. ^[68]
<i>Acorus calamus</i> Acoraceae (Araceae)	Sweet flag, Vacha	Rhizome	Cineole, Beta-asarone, Azulene	Used as tranquilizer. Sharpen memory, awareness and increase circulation to the brain. ^[69]

Future treatment breakthrough

Alzheimer's disease is an irreversible, progressive brain disorder related to changes in nerve cells that result in the death of brain cells and one of the foremost health troubles observed in old peoples. Researchers are looking for new ways to treat Alzheimer's. Current drugs help mask the symptoms of Alzheimer's, but do not treat the underlying disease or delay its progression. A breakthrough Alzheimer's drug would treat the underlying disease and stop or delay the cell damage that eventually leads to the worsening of symptoms. There are several promising drugs in development and testing, but we need more volunteers to complete clinical trials of those drugs and increased federal funding of research to ensure that fresh ideas continue to fill the pipeline.

CONCLUSION

This review summarizes information concerning the all aspects of cellular activities and disease progression of Alzheimer's disease in order to provide sufficient baseline information that could be used in drug discovery campaigns and development process, thereby providing new functional leads for Alzheimer's disease. Research on various latest technologies that have shown promise in reversing the Alzheimer's disease pathology.

The above mentioned studies suggest that the treatment strategies for the management of patients with Alzheimer's disease will have to include a variety of interventions directed at multiple targets. The presently available allopathic drugs approved by Food and Drug Administration (FDA), USA have not offered satisfactory solution for the treatment & complete cure of the disease and they produce various side effects and are often too costly. Moreover, these drugs are symptomatic and do not alter the course or progression of the underlying disease.

This warrants for the exploration of better therapeutics with least side effects for the treatment and management of this disease. Thus, multidisciplinary investigations on alternative natural treatments described above as well as herbal remedies needed in order to develop effective therapeutic protocols for the management of the Alzheimer's disease.

In this review article, an attempt has been made to give the information about the cellular activities in disease progression and also compile the various reported neuroprotective agents which may be useful to the health professionals, scientists and scholars working the field of pharmacology and therapeutics to develop evidence based alternative medicine to cure different kinds of neuronal diseases in man and animals.

REFERENCES

1. Brookmeyer R., Gray S., Kawas C. "Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset".

- American Journal of Public Health. 1998; 88(9): 1337-42.
2. Berchtold NC, Cotman CW. "Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s". Neurobiol. Aging. 1998; 19(3): 173-89.
3. Waldemar G, Dubois B, Emre M, et al. "Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline". Eur J Neurol. 2007; 14(1): 1-26.
4. Tabert MH, Liu X, Doty RL, Serby M, Zamora D, Pelton GH, Marder K, Albers MW, Stern Y, Devanand DP. "A 10-item smell identification scale related to risk for Alzheimer's disease". Ann. Neurol. 2005; 58(1): 155-160.
5. Tiraboschi P, Hansen LA, Thal LJ, Corey-Bloom J. "The importance of neuritic plaques and tangles to the development and evolution of AD". Neurology. 2004; 62(11): 1984-9.
6. Blanchard BJ, Hiniker AE, Lu CC, Margolin Y, Yu AS, Ingram VM. "Elimination of Amyloid beta Neurotoxicity". J Alzheimers Dis. 2000; 2(2): 137-149.
7. Berchtold NC, Cotman CW. Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s. Neurobiol Aging 1998 May-Jun; 19(3): 173-89.
8. Yankner BA. Mechanisms of neuronal degeneration in alzheimer's disease. Neuron. 1996; 16: 921-932.
9. Bell KF, Claudio Cuello A. Altered synaptic function in Alzheimer's disease. Eur J Pharmacol. 2006; 545: 11-21.
10. Citron M. Alzheimer's disease: strategies for disease modification. Nat Rev Drug Discov. 2010; 9: 387-398.
11. Heininger K. A unifying hypothesis of Alzheimer's disease. II. Pathophysiological processes. Hum Psychopharmacol Clin Exp. 1999; 14: 525-581.
12. Braak H, Braak E, Yilmazer D, Devos RAI, Jansen ENH, Bohl J, et al. Amygdala pathology in parkinson's disease. Acta Neuropathol. 1994; 88: 493-500.
13. Morris RG. The memory deficits in Alzheimer-type dementia: a review. Q J Exp Psychol. 1986; 38A: 575-602.
14. Blanchard BJ, Chen A, Rozeboom LM, Stafford KA, Weigle P, Ingram VM. "Efficient reversal of Alzheimer's disease fibril formation and elimination of neurotoxicity by a small molecule". Proc. Natl. Acad. Sci. U.S.A. 2004; 101(40): 14326-32.
15. Nitta A., Itoh A., Hasegawa T., Nabeshima T. β -Amyloid protein-induced Alzheimer's disease animal model. Neurosci. Lett. 1994; 170: 63-66.
16. Nitta A., Fukuta T., Hasegawa T., Nabeshima T. Continuous infusion of β -amyloid protein into cerebral ventricle induces learning impairment and neuronal and morphological degeneration. Jpn. J. Pharmacol. 1997; 73: 51-57.

17. Brion JP The role of neurofibrillary tangles in Alzheimer disease. *Acta Neurol Belg.* 1998; 98: 165-174.
18. Games D., Khan K.M., Soriano F.G., Keim P.S., Davis D.L., Bryant K., Lieberburg I. Lack of Alzheimer pathology after beta-amyloid protein injections in rat brain. *Neurobiol. Aging.* 1992; 13: 569-576.
19. Kang J., Lemaire H.G., Unterbeck A., Salbaum J.M., Masters C.L., Grzeschik K.H., Multhaup G., Beyreuther K., Muller-Hill B. The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. *Nature.* 1987; 325: 733-736.
20. Frederick A. Schmitt, Christine H. Wichems. A Systematic Review of Assessment and Treatment of Moderate to Severe Alzheimer's disease. *Prime Care Companion J Clin Psychiatry.* 2006; 8(3): 158-159.
21. Nabeshima T., Tohyama K., Murase K., Ishihara S., Kameyama T., Yamasaki T., Hatanaka S., Kojima H., Sakurai T., Takasu Y., Shiotani T. Effects of DM-9384, a cyclic derivative of GABA, on amnesia and decrease in GABA_A and muscarinic receptors induced by cycloheximide. *J. Pharmacol. Exp. Ther.* 1991b; 257: 271-275.
22. Anil Kumar, Arti Singh. A review on Alzheimer's disease pathophysiology and its management: an update. *Ekavali Pharmacological Reports*, April 2015; 67(2): 195-203.
23. Daniel P. Perl, *Neuropathology of Alzheimer's disease Mt Sinai J Med.* 2010 Jan-Feb; 77(1): 32-42.
24. Storey E., Kinsella GJ, Slavin MJ The neuropsychological diagnosis of Alzheimer's disease. *J Alzheimers Dis.* 2001; 3: 261-285.
25. Wojciech Danysz and Chris G Parsons. Alzheimer's disease, β -amyloid, glutamate, NMDA receptors and memantine – searching for the connections, *Br J Pharmacol.* 2012 Sep; 167(2): 324-352.
26. Wenk GL. Neuropathologic changes in Alzheimer's disease: potential targets for treatment. *J Clin Psychiatry.* 2006; 67(Suppl. 3): 3-7.
27. Sorrentino G., Bonavita V. Neurodegeneration and Alzheimer's disease: the lesson from tauopathies. *Neurol Sci.* 2007; 28: 63-71.
28. Hof PR, Glannakopoulos P., Bouras C. The neuropathological changes associated with normal brain aging. *Histol Histopathol.* 1996; 11: 1075-1088.
29. SYMPTOMS & brain imaging Alzheimer's disease: A Clinical and Basic Science Review Igor O. Korolev* *Medical Student Research Journal MSRJ #* 2014 VOL: 04. Issue: Fall epub September 2014; 24-33.
30. Goedert M. Tau protein and the neurofibrillary pathology of Alzheimer's disease. *Trends Neurosci.* 1993; 16: 460-465.
31. Goedert M. Tau protein and the neurofibrillary pathology of Alzheimer's disease. *Trends Neurosci.* 1993; 16: 460-465.
32. Zhang L., Song L., Terracina G., et al. Biochemical characterization of the gamma-secretase activity that produces beta-amyloid peptides. *Biochemistry.* 2001; 40: 5049-5055.
33. Holmes C, Ballard C, Lehmann D, et al., Rate of progression of cognitive decline in Alzheimer's disease: effect of butyrylcholinesterase K gene variation, *J Neurol Neurosurg Psychiatry,* 2005; 76(5): 640-43.
34. Doecke JD, Laws SM, Faux NG, Wilson W, Burnham SC, Lam CP, et al. Blood-based protein biomarkers for diagnosis of Alzheimer disease. *Arch Neurol* 2012; 69: 1318-25.
35. Vemuri P, Wiste HJ, Weigand SD, Shaw LM, Trojanowski JQ, Weiner MW, et al. MRI and CSF biomarkers in normal, MCI, and AD subjects: diagnostic discrimination and cognitive correlations. *Neurology* 2009; 73: 287-93.
36. Keith A. Johnson, Nick C. Fox, Reisa A. Sperling and William E. Klunk. *Brain Imaging in Alzheimer Disease: Cold Spring Harb Perspect Med.* 2012 Apr; 2(4): 006213.
37. Philip Scheltens, *Imaging in Alzheimer Disease, Dialogues Clin Neurosci.* 2009 Jun; 11(2): 191-199.
38. Agneta Nordberg. *Molecular imaging in Alzheimer's disease: new perspectives on biomarkers for early diagnosis and drug development: Alzheimers Res Ther.* 2011; 3(6): 34.
39. Beckett TL, Webb RL, Niedowicz DM, Holler CJ, Matveev S, Baig I, Le Vine H et al. Postmortem Pittsburgh Compound B (PiB) binding increases with Alzheimer's disease progression: *J Alzheimers Dis.* 2012; 32(1): 127-38.
40. Ronald C. Petersen, MD Glenn E. Smith, Stephen C. Waring et al. *Mild Cognitive Impairment Clinical Characterization and Outcome: Arch Neurol.* 1999; 56(3): 303-308.
41. Lonneborg A. Biomarkers for Alzheimer disease in cerebrospinal fluid, urine and blood *Mol Diagn Ther.* 2008; 12(5): 307-20.
42. Xiao Ling Li, Nan Hu, Meng Shan tan, Jin Tai Yu and Lan Tan. *Behavioral and Psychological Symptoms in Alzheimer's disease: Bio Med Research International,* 2014; (2014): 1-9.
43. Yiannopoulou K., Karydakis K., Sakka P. (2009) *Therapeutic targets in Alzheimer's disease. Primary Psychiatry* 16: 29-36.
44. Churcher I. *Tau therapeutic strategies for the treatment of Alzheimer's disease. Curr Top Med Chem.* 2006; 6: 579-595.
45. Konstantina G. Yiannopoulou and Sokratis G. Papageorgiou. *Current and future treatments for Alzheimer's disease Ther Adv Neurol Disord.* 2013 Jan; 6(1): 19-33.
46. Van Marum RJ. *Current and future therapy in Alzheimer's disease. Fundam Clin Pharmacol:* 2008 Jun; 22(3): 265-74.
47. Bullock R. *Drug treatment in dementia: Curr Opin Psychiatry* 2001; 14: 349-353.
48. Cummings J, Winblad B. *A rivastigmine patch for the treatment of Alzheimer's disease and Parkinson's*

- disease dementia: *Expert Rev Neurother.* 2007 Nov; 7(11): 1457-63.
49. Amanatkar HR, Grossberg GT. Transdermal Rivastigmine in the treatment of Alzheimer's disease: current and future directions. *Expert Rev Neurother.* 2014 Oct; 14(10): 1119-25.
 50. Birks J, Grimley Evans J, Iakovidou V, Tsolaki M, Rivastigmine for Alzheimer's disease, *Cochrane Database Syst Rev*, 2000; 4: CD001191.
 51. Lefèvre G, Sedek G, Huang HL, et al., Pharmacokinetics of a rivastigmine transdermal patch formulation in healthy volunteers: relative effects of body site application, *J Clin Pharmacol*, 2007; 47(4): 471-8.
 52. Lefèvre G, Sedek G, Jhee S, et al., Pharmacokinetics and pharmacodynamics of the novel daily rivastigmine transdermal patch compared with twice-daily capsules in Alzheimer's disease patients, *Clin Pharm Ther*, 2008; 83(1): 106-14.
 53. Corbett A, Williams G, Ballard C. Drug repositioning: an opportunity to develop novel treatments for Alzheimer's disease. *Pharmaceuticals* 2013; 6: 1304-21.
 54. Brendan J. Kelley, David S. Knopman. *Alternative Medicine and Alzheimer's disease: Neurologist.* 2008 Sep; 14(5): 299-306.
 55. Singh N, Chhillar N, Banerjee B., Basu K., Mustafa M. Organochlorine pesticide levels and risk of Alzheimer's disease in north Indian population. *Hum Exp Toxicol*: 2013 Jan; 32(1): 24-30.
 56. Moriyama Y, Mimura M, Kato M, Kashima H. Primary alcoholic dementia and alcohol-related dementia. *Psychogeriatrics*. 2006; 6: 114-118.
 57. Lane RM, Potkin SG, Enz A, Targeting acetylcholinesterase and butyrylcholinesterase in dementia, *Int J Neuropsychopharmacol*, 2006; 9(1): 101-24.
 58. Nicole J Ridley, Brian Draper and Adrienne Withall. Alcohol-related dementia: an update of the evidence: *Alzheimers Res Ther.* 2013; 5(1): 3.
 59. Walton JR. Aluminum involvement in the progression of Alzheimer's disease: *J Alzheimers Dis.* 2013; 35(1): 7-43.
 60. Soni M, Kos K, Lang IA, Jones K, Melzer D, Llewellyn DJ. Vitamin D and cognitive function. *S Chand J Clin Lab Invest Suppl.* 2012; 243: 79-82.
 61. An Overview of Phytotherapeutic Approach in Prevention and Treatment of Alzheimer's Syndrome & Dementia Narendra Singh*, B. R. Pandey, Pankaj Verma, *International Journal of Pharmaceutical Sciences and Drug Research* 2011; 3(3): 162-172.
 62. K.Yalla Reddy, 1S. Mohana Lakshmi, 1A. Saravana Kumar. Review On Effect Of Natural Memory Enhancing Drugs On Dementia *International Journal of Phytopharmacology*, 2010; 1(1): 1-7.
 63. Anonymous. *Indian Pharmacopoeia.* Indian Pharmacopoeia Committee Ministry of Health and Family Welfare, Government of India: New Delhi; (1996).
 64. Saini K, Chaudhary A, Sharma RK. Effect of *Celastrus paniculatus* on Learning, Memory and Serum Biochemistry of Aging Albino Rats. *Indian Journal of Gerontology* 2006; 20(4): 310-316.
 65. Vallejo MG, Ortega MG, Cabrera JL, Carlini VF. Rubiales de Barioglio S, A.M. Agnese, Huperzia Saururus increases memory retention in rats. *Journal of ethnopharmacology*, 2007; 111: 685-687.
 66. TSai TH, Wetly I, Lee TF, Chen CF, Wang LCH. Effects of Honokiol and magnolol on acetylcholine release from rat hippocampal slices. *Plant med.*, 1995; 61: 477-479.
 67. Khory RN, Katrak NN. *Materia Medica and Their Therapeutics.* Neeraj Publishing House, Delhi, 1981.
 68. Exploration of natural compounds as sources of new bifunctional scaffolds targeting cholinesterases and beta amyloid aggregation: The case of chelerythrine Gerda Brunhofer a, Adyary Fallarero a, Daniela Karlsson a, Ana Batista-Gonzalez a, Pravin Shinde b, C. Gopi Mohan b, Pia Vuorela a,! *Bioorganic & Medicinal Chemistry* 2012; 20: 6669-6679.
 69. Singh N. and Gilca M. *Herbal Medicine – Science embraces tradition – a new insight into the ancient Ayurveda.* Lambert Academic Publishing (Germany). 2010; 520-535.