International Journal of Pharma and Bio Sciences V1(2)2010

ALZHEMIER'S DISEASE – PATHOPHYSIOLOGY AND TREATMENT

ASMA SHAHEDA SHAIK [1], A. ELAYA RAJA[1*], M.VIJAYALAKSHMI[2] AND G.DEVALARAO[1]

1. **KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada-520010.**
2. **Department of Microbiology, Acharya Nagarjuna University, Nagarjuna nagar, Guntur-522510.**

Corresponding Author elayaraja80@rediffmail.com

ABSTRACT

Alzheimer's disease is one of a slow dreadful disease which is affecting only from the adulthood upto aged people on nervous systems present in brain. In this present review article, the history, pathology, theories, hypothesis, factors, major symptoms and associated symptoms of this particular disease, stages of the disease, diagnosis and current treatment of the disease have been explained neatly and legibly with proper diagrams which is easy to understand. The legends introduced in this topic are very easy to know the reasons for this disease and how to control from its bad effects is also given. Some essential treatments are revealed here which paves a good way to prevent this dreadful disease and its conditions. Finally a discussion is also given to regulate the proper care giving to the affected people who are basically on humanitarism background.

KEY WORDS

Alzheimer, dementia, pathology, diagnosis, therapy.

INTRODUCTION

Alzheimer's disease is a progressive form of dementia which occurs from middle age to old age. It is the fourth leading cause of death among 10% of 70 years[1] aged people after myocardial infraction, stroke and cancer. It is a neurons degenerative disorder which is characterized by progressive and irreversible loss of memory and nonvascular dementia[2-3] due to the destructive function of cholinergic neurons[4] distributed in the specific regions of brain such as hippocampal and cortical areas. The main clinical feature of this disease is the impairment of memory, short term memory and cognitive disability. As the condition progresses, additional cognitive abilities are impaired such as the ability to calculate, visuospatial skills and ideomotor apraxia[5]. In the advance stage, motor weakness increases that leads to muscular contractures which produces immobility such as pneumonia, pulmonary embolism and death. At present no direct ante mortem confirmatory test exists. Although the risk of developing Alzheimer's disease increases with age – in most people, symptoms first appear after age 60[6]. Alzheimer's disease is not a part of normal aging. It is caused by a fatal disease that affects the brain (fig-1).

HISTORY OF THE DISEASE

Alzheimer Disease (AD) is the most common cause of dementia among people of elder age of 65 and above. It was investigated and named by Alois Alzheimer and his coworkers in 1906. Scientists estimate that around 35 million people now have Alzheimer Disease world wide. In India one part of Indians are affected at present[7]. For every 5-year age group beyond 65, the percentage of people with AD

ALZHEMIER'S DISEASE – PATHOPHYSIOLOGY AND TREATMENT

doubles. By 2050, 107 million of people will be affected world wide.

MAJOR SYMPTOMS OF ALZHEIMER'S DISEASE

While deterioration of brain function takes the spot light in Alzheimer patients there are various body and mind related problems[8] started to produce. They are as follows:

Sleep patterns: Normal sleep is a major problem in these types of patients. Many Alzheimer patients suffer from abnormal sleep patterns. They are wandering during the night around the berth place and sleeping during the day time. Normal sleep patterns are restored in the Alzheimer's patient by treating them with serotonin and dopamine optimization.

Inappropriate anger, aggression or yelling out: This is another major problem with some Alzheimer patients. This is also overcome by treating them with anxiolytic agents combining with serotonin and dopamine optimization which checks an inappropriate anger, aggression or yelling out from those patients.

Agitation: Many Alzheimer patients are suffering from inappropriate agitation. This may take the form of mental or physical agitation. This is overcome by treatment with antianxiety agents on combined treatment with Anti-alzheimer drug therapy.

Depression: It is common in Alzheimer's patients. Depression displays in the form of an agitated depression. In medicine there is no proper drug that effectively controls depression in the elder patients with Alzheimer.

Anxiety: In general is present in Alzheimer's patients. With neurotransmitter optimization of serotonin and dopamine guided by neurotransmitter testing as indicted, anxiety in the Alzheimer patient may be controlled.

Psychotic state: It is a significant problem with patients talking about and hearing or seeing things that are not there. This is overcome by combination treatment with Antipsychotic agents or neuroleptic agents with Anti-alzheimer drug therapy.

Restless Leg Syndrome: It is common and mostly contributed in creating the sleeping disturbance which leads to exacerbation of cognitive problems. With neurotransmitter optimization of serotonin and dopamine guided by neurotransmitter testing as indicted, Restless Leg Syndrome[9] in the Alzheimer patient can be controlled.

ASSOCIATED SYMPTOMS OF ALZHIEMER'S DISEASE

Apart from major symptoms, two symptoms are playing a vital role which is associated with Alzheimer's disease. The primary symptom of Alzheimer's disease is cognitive type of symptoms. They are Amnesia (short term and long term memory loss), aphasia, agnosia and apraxia[10].The secondary symptom of Alzheimer's disease is psychiatric type of symptoms. They are personality changes, depression, hallucinations and delusions.

PATHOLOGY OF ALZHEIMER'S DISEASE

Dating back to Alois Alzheimer in 1907 initial description of the disease are the characteristic silk-like senile plaques and neurofibrillary tangles[11] which threads that accumulate within the gray matter of the cerebral cortex and cerebral nerve cells of Alzheimer patients (fig 2). This produces the cerebral arterioclerosis[12-13] which is responsible for loss of memory in presenile dementia of Alzheimer. This affected part is composed of highly indigestible amyloid fibers, Alzheimer patients are unable to break these fibers down and produces hippocampus (fig 3).Glenner explained that accumulation of these fibers leads to the production of the brain lesions which are the basic characteristic of this disease. Also he

reported that the plaques accumulate to neurotoxic levels, compressing those nerve fibers which are laying in their path and destroy these regions very effectively in the brain. This destruction of cerebral tissue then causes the behavioral changes which are associated with Alzheimer's dementia. In extremely progressed cases, these amyloid fibers will aggregate around blood vessels, causing a structural weakening to occur in the vessels and a subsequent leakage of blood serum into the cerebral space. If leakage is great, intercerebral hemorrhage and stroke are likely to occur.

THEORIES OF ALZHEIMER'S DISEASE[14-15]

Five theories are warrant to determine the actual cause of this disease:

1. Chemical Theory:

Biochemical Deficiencies: Brain cells communicate with each other through biochemical substances called as neurotransmitters. Studies of Alzheimer's diseased brains have uncovered diminished levels of various neurotransmitters that are thought to influence intellectual functioning and behavior.

Toxic Chemical Excesses: Increased deposits of metal ions such as aluminum, Lead, etc have been found in Alzheimer's disease brains.

2. Genetic Theory:

This theory explains the inheritance of a gene which directs the production of apolipoprotein (ApoE).In early-onset Alzheimer's, mutation on chromosome 14 which accounts for 10% of Alzheimer's cases. Additionally, a mutation was also found out on chromosomes 1 and 21. In 1997, another mutation on chromosome 12 effectively linked to late-onset Alzheimer's.

3. Autoimmune Theory:

The body's immune system, which protects against potentially harmful invaders, may erroneously begin to attack its own tissues, producing antibodies to its own essential cells.

4. Slow Virus Theory.

A slow-acting virus has been identified as a causative agent for Alzheimer's disease.

5. Blood Vessel Theory.

Defects in blood vessels supplying blood to the brain are being studied as a possible cause of Alzheimer's.

HYPOTHESIS OF THE DISEASE

Various hypothesis also explains about the cause for that disease. They are as follows.

1. Cholinergic hypothesis: This hypothesis states that the reduction in synthesis of cholinergic neurotransmitter Acetylcholine[16-18] causes Alzheimer's disease. Due to the neurotransmitter reduction disruption of neuronal circuits (fig 4) takes place in cortical and basal ganglia of brain.
2. Amyloid Hypothesis: Amyloid precursor protein (APP) is the precursor to amyloid plaque. APP sticks through the neuronal membrane. But some enzymes (Chaperone enzymes) cut the APP into fragments of protein, including beta-amyloid. β-amyloid fragments (fig 5) come together in clumps to form senile plaques in substantia nigra. These clumps disrupt the work of neurons that affects the hippocampus and other areas of the cerebral cortex[19-20].
3. Tau Hypothesis: Neurons have an internal support structure partly made up of microtubules. A protein called *tau* helps to stabilize these microtubules. In Alzheimer's disease, *tau*[21-25] produces change in microtubules to collapse, devastate and clump the

neural active proteins together to form neurofibrillary tangles (fig 6) and senile plaques.

FACTORS OF ALZHIEMER'S DISEASE

The chances of getting Alzheimer's disease increases with age and it usually occur after the age of 65, after which the chances of getting the disease double every five years. There are only two definite factors which increase the risk for Alzheimer's disease before age 65. The primary factor is the family history of dementia (Vascular dementia and Lewy body dementia) and Alzheimer's which is already prevailing in the heredity[26]. The second factor is the Down's syndrome[27]. Down syndrome is defined as a combination of physical abnormalities and mental retardation characterized by a genetic defect in chromosome pair 21.

VARIOUS STAGES OF THE DISEASE[29-33]

STAGE-I (Pre-Dementia):-A mild cognitive symptom which occurs in the initial stage within 2 months and is observed by the following actions such as attentiveness, planning, abstract thinking and semantic memory (fig 7).

STAGE-II (Early-Dementia):- This is a moderate cognitive symptom which occurs after 20 years period before diagnosis and is observed by the following conditions such as impairment of learning, memory, fine motor tasks, language problems, episodic memory and vocabulary problems (fig 8a).

STAGE-III (Moderate-Dementia):- This is advance stage of moderate cognitive symptom which occurs for a period of 1 to 5 years and is observed by the following conditions such as progressive deterioration, increase in vocabulary problems, worsening of memory problems, wandering, sundowning, anognosia and urinary incontinence(fig 8b).

STAGE-IV (Advanced-Dementia):- This is a complete stage for a period above 10 years and is completely dependence on care givers. It is the mature stage of the disease which is observed by the following conditions such as bed ridden, unable to eat and g.i.t. internal problems (ulcer formation and pneumonia) (fig 8c).

ALZHEMIER'S DISEASE – PATHOPHYSIOLOGY AND TREATMENT

Various figures showing the spreading and producing apoptosis to the brain in Alzheimer's disease

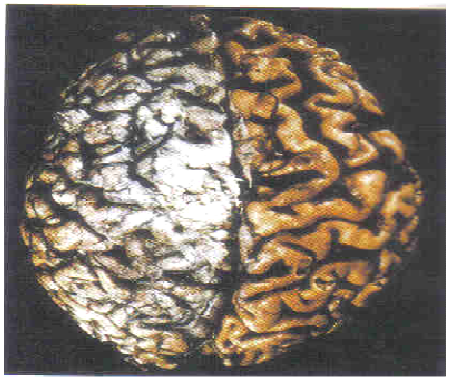

Fig 1: Alzheimer's disease with cortical atrophy most evident on the right where meninges have been removed due to degeneration of nerves.

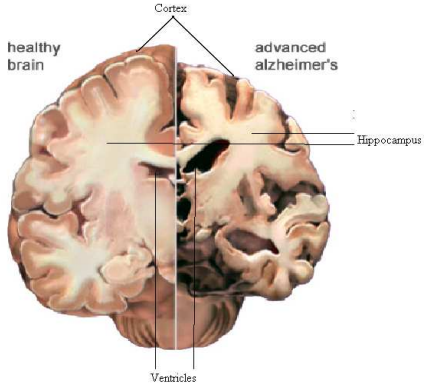

Fig 2: Various features in Alzheimer's brain then healthy brain are cortex shrivels up, shrinkage of hippocampus and larger growth of ventricles.

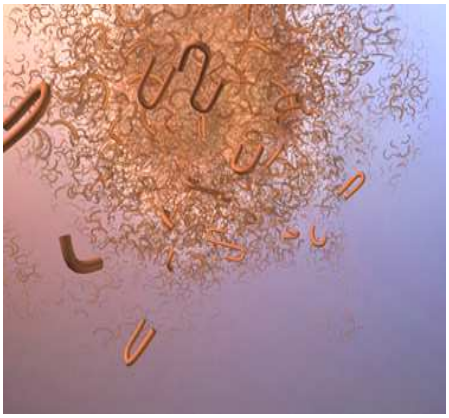

Fig 3: Plaques form when protein pieces called β-amyloid proteins degraded and clump together.

ALZHEMIER'S DISEASE – PATHOPHYSIOLOGY AND TREATMENT

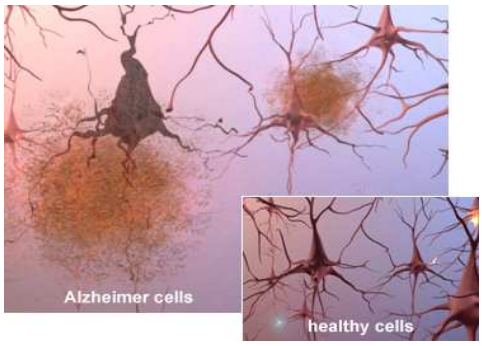

Fig 4: Alzheimer tissue has many fewer nerve cells and synapses than a healthy brain. Plaques and abnormal clusters of protein fragments, build up between nerve cells. Dead and dying nerve cells contain tangles, which are made up of twisted strands of another protein reduction of neurotransmission.

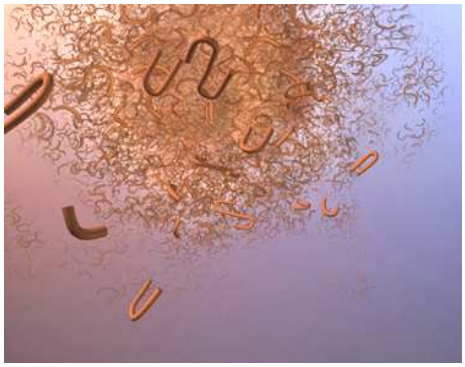

Fig 5: Plaques form when protein pieces called β-amyloid proteins degraded and clump together.

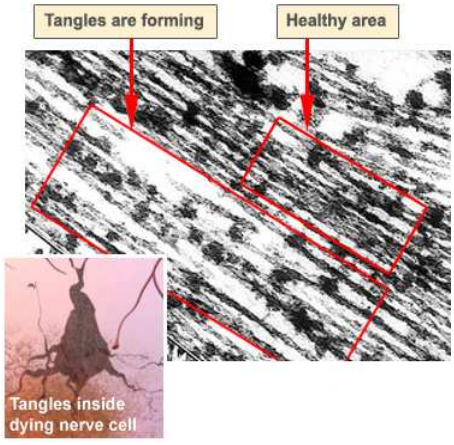

Fig 6: A protein called tau produce tangles and collapses twisted strands.

ALZHEMIER'S DISEASE – PATHOPHYSIOLOGY AND TREATMENT

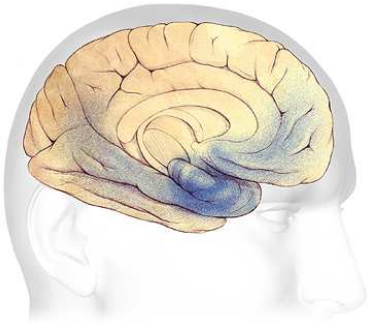

Fig 7: Mild to moderate Alzheimer's Plaques and tangles (blue shaded) started spreading to all areas of brain.

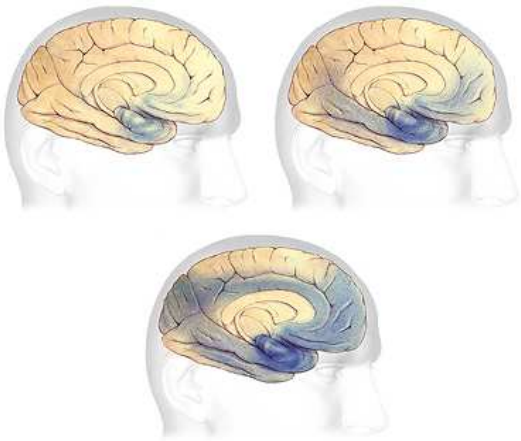

Fig 8: 8a. Early dementia- changes begins 20 years before diagnosis.
8b. Moderate dementia-2 to 10 years.
8c. Advances dementia- above 10 years.

STUDIES OF ALZHEIMER'S DISEASE AT THE CELLULAR AND MOLECULAR LEVEL

Oxidative damage from free radical molecules injures the neurons present in brain and hippocampus. In general, homocysteine, an amino acid, is a risk factor for heart disease. A study shows that an elevated level of homocysteine[34-35] in brain is also associated with increased state of risk for Alzheimer's disease. Scientists also declared that inflammation in certain regions of the brain and strokes of the cerebro spinal fluid also considered as risky factors for Alzheimer's disease.

DIAGNOSING OF ALZHEIMER'S DISEASE

Alzheimer's disease is diagnosised today by using a number of biochemical and genetic tools. Various steps has been followed to diagnosis[36] the disease and its primary or secondary symptoms. They are as follows.

1. A detailed patient history.
2. Information from family and friends regarding the subject.

3. Physical and neurological exams [37]and lab tests of the subject.
4. Neuropsychological tests about the subjects behavior.
5. PET scans are first used at present in the initial stage. Also imaging tools of the subjects brain such as CT scan, magnetic resonance imaging (MRI), Neuronal Amplitude measuring instrument[38] are also employed on examination time

CURRENT TREATMENT FOR ALZHEIMER'S DISEASE

Alzheimer's disease is a progressive and debilitating disease that affects many of us, either directly or through someone we know, yet science has still not revealed a cure. Several compounds are being currently tested to prevent and treat the disease. Some current methods of treatment of Alzheimer's disease have been explored[39]. They are as follows:

1. Cholinoceptors Pathway Degeneration[40-47]

Anticholinergic drugs such as anticholinesterase inhibitors (Rivastigmine, Physostigmine, Neostigmine and Pyridostigmine) has shown good efficacy in improving the cognitive function in Alzheimer type dementia. Their use is limited because of short half life and systemic cholinergic actions. Amino acridines are playing a vital role in preventing the Alzheimer's disease and its symptoms[48]. Tacrine is another anticholinergic drug which inhibits both acetyl cholinesterase and butyryl cholinesterase enzymes which inhibits the effects promoted by M_1 and M_2 cholinoceptors. Velnacrine, a cholinomimetic analog of tacrine is currently under investigation. Donepezil[49] is another acetyl cholinesterase inhibitor which is presently available.

2. N-methyl-D-Aspartate (NMDA) Pathway Degeneration[50]

Over stimulation of N-methyl-D-Aspartate (NMDA) produces excitotoxic effects on neurons which further produces neurodegenerative processes. This problem is overcome by treatment with amantadine derivatives such as Memantine (dimethyl adamantine) which is an uncompetitive inhibitor of NMDA receptors.

3.Antioxidants[51]

The brain has high oxygen consumption rate and abundant poly unsaturated fatty acids in the neuronal cells. If the neuronal cells get free radical damage, it results in cognitive decline and neurodegenerative diseases (Alzheimer's disease). In this case antioxidants such as vitamin-E (α-tocopherol) monoamino oxidase inhibitor (selegiline)[52-53], phenolics (curcumin), tannins (gallic acid) and polyphenolics (ferulic acid) reduce the free radical formation and prevents the cognitive syndromes.

4. Vaccination [54]

Several vaccines are under development to reduce the cognitive symptoms due to Alzheimer's disease. These vaccines stimulate the immune system to produce antibodies against the pathogens which create the problem. The vaccine is injected in the form of β-amyloid that clear the plaques and physical signs of Alzheimer's disease. One of the developed vaccines administered by intramuscular route is AN-1792 which produces nonfatal inflammation, improvement and recovery from symptoms of Alzheimer's disease. Another one is developed in the modified form of amyloid protein administered by nasal route.

5. Estrogen therapy

Research work shows that postmenopausal hormone therapy increases the risk of dementia in

healthy women. In these circumstances estrogen after administration improves the cognitive function. In this case raloxifene which is a selective estrogen receptor modulator reduces the risk of dementia in Alzheimer's disease (Research approach from University of Wisconsin). The National Institute of aging also prescribed regarding the estrogen patch which is a sustained release to reduce the risks of Alzheimer's disease.

6. Implanting Healthy Neurons

Cognitive problems are stem from low levels of acetylcholine. Transplanting healthy cholinergic neurons (cholinoceptors) into the brain would be a direct way to restore acetylcholine levels. Stem cells having cholinoceptors is also produce healthy levels of acetylcholine which prevents neurodegenerative diseases (Alzheimer's disease).

7. Support from caregivers[55]

Spouses are the largest group of care giving. But most of the spouses are older with their own health problems. Hence sons and daughters are the second largest group for take care of them. They are commonly called as "Sandwich Generation" because many are married and raising children of their own. Those children need extra support if a parent's attention is focused on care giving. In that case grandchildren may become the major helpers for them. Daughters-in-law – the third largest group. For the old age people their brothers and sisters are also older and also have their own health problems. The next groups are their friends, neighbors and members of their faith community who are in the same platform.

RESULTS AND DISCUSSIONS

From our studies a detailed manner of various informations from various sources had been reviewed and submitted. However, while many researchers are devoting a lot of time and resources in finding a treatment that will ameliorate Alzheimer, no treatment has, as of yet, been completely successful. Future trends of researchers are investigating on the antioxidants to reduce the stress and its development into dementia which further paves the way to produce cognitive disorders such as Parkinsonism, Alzheimer's disease, etc. Many neurotropic drugs and nootropic agents[1] had been employed so far and still on evaluation from plant sources to reduce the apoptosis of neural cells in the cholinergic nervous system which is a major originator for acetylcholine. Also to prevent the amyloid deposition antiamyloid therapy is also under investigation. An adjuvant therapy such as channel blockers has also been employed to prevent overloading of ca^{2+} ions in neurons. Introduction of minerals such as calcium, magnesium, sodium comprising the natural foods[2] such as pulses, green vegetables, beans and other protein containing eatables increase the constructive nature of the human brain cells in future.

REFERENCES

1. Harrison TR and Peterdsdoff RG. Harrison's principles of Internal Medicine. MC Graw Hill Publishers, London. Vol-II. 2008: 2539.
2. Katzung BG. Basic and Clinical Pharmacology. In: Special acpects of geriatric pharmacology. Prentice Hall International Publishers. 1995:6th edn; 927.
3. Knopman DS *et al*., Incidence and causes of nondegenerative nonvascular dementia: A population based study. Arch Neurol. 2006: 63; 218.
4. Chaudhuri SK. Quintessence of Medical Pharmacology. In: Central Nervous system.1997: 1st edn; 155.

ALZHEMIER'S DISEASE – PATHOPHYSIOLOGY AND TREATMENT

5. Cummings JL. Dementia. In: The failing brain. Lancet. 1995: 345; 1481-1484.
6. Gooch MD and Stennett DJ. Molecular basis of Alzheimer's disease. *Am J Health-Syst Pharm*. 1996: 53; 1545-1547.
7. www.your total health .com-page 1-4.
8. www.neurologychannel.com/Alzheimer/index.5HTML
9. www.ALZinfo.org/pp1-4.
10. Stahl SM. Essential Psychopharmacology. In: Cognitive enhancers and neuroprotective agents. Cambridge University Press, 1st edn.1998: 293.
11. Hardman GJ and Limbird LE. The Pharmacological basis of Therapeutics. In: Treatment of central nervous system degenerative disorders. 1996: 9th edn; 513-514.
12. Das PK and Bhattacharya SK. Pharmacology. In: Central Nervous system. BI Churchill Livingstone Pvt Ltd. 1995:1st edn; 282.
13. Van Oijen M *et al*. Artherosclerosis and risk for dementia. *Ann Neurol*. 2007:61; 403.
14. www.encyclopedia.org/Alzheimer_disease.5-6 pdf form.
15. www.wikipedia.org/wiki/ Alzheimer_disease.1-4 DOCXform.
16. Lewis DA and Bloom Fe. "Clinical Perspectives on neuropeptides". *Annu Rev Med*, 1983: 23; 143.
17. Johnston MV. Cognitive disorders. In: Principles of drug therapy in Neurology. F.A.Davis Publications, Philadelphia, 1992: 226-267.
18. Perry EK.The cholinergic hypothesis-ten years on. *Brit Med Bul*, 1986: 42; 63-69.
19. Textbook of Medical Biochemistry, MN Chatterjea and Rana Shinde, 6th edition, 2005: 87; 241-242.
20. Yankner BA, Duffy LK and Kirschner DA. Neurotrophic and Neurotoxic effects of amyloid β protein: reversal by tachykinin neuropeptides, *Science*, 1990: 250&279.
21. Arnold SE, *et al***.** The topographical and neuro anatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. Cereb. Cortex, 1991:1; 103-116.
22. Arrigada PV, *et al*. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurol*. 1992: 42; 631-639.
23. Braak H and Braak E. Pathology of Alzheimer's disease. In: Neurodegenerative diseases.W.B. Saunders Publications, Philadelphia. 1994: 585-614.
24. Small GW et al. PET of brain amyloid and tau in mild cognitive impairment. *N Engl J Med*. 2007: 355; 2652.
25. www.medicalnewstoday.com/articles/9170.php
27. www.wikipedia.org/wiki/ Alzheimer_disease.8-10 pdf form
28. Martindale–The complete drug Reference. British Pharmaceutical Press. In: Parasympathomimetics. 1412.
29. www.alz.org/braintou1asp.HTML
30. www.alz.org/braintou2asp.HTML
31. www.alz.org/braintou3asp.HTML
32. www.alz.org/braintou4asp.HTML
33. www.alz.org/braintou5asp.HTML
34. www.nia.nih.gov/alzheimer's disease1HTML
35. www.nia.nih.gov/alzheimer's disease2HTML
36. www.alzheimer's.about.com-diagnosis index.5html
37. www.ahaf.org/ Alzheimer's.com.pp1-4.
38. Gottlieb GL and Kumar A. Conventional pharmacologic treatment for patients with Alzheimer's disease. *Neurol*.1993: 43(suppl 4); S56.
39. Arrigada PV *et al*. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurol*. 1992: 42; 631-639.

40. Culter NR and Sramek JJ. Muscarinic M1 receptor agonists-potential in the treatment of Alzheimer's disease. CNS Drugs. 1995: 3; 467-469.
41. Eagger SA, *et al*. Tacrine in Alzheimer's disease. *Lancet*. 1991:337; 989-992.
42. Knapp MJ, et al. A 30 week randomized controlled trial of high dose tacrine in Patients of Alzheimer's disease. JAMA. 1994: 271; 985-987.
43. Levy R. Tacrine and Lecithin in Alzheimer's disease. *Br.Med.J*. 1990: 300; 939- 940.
44. Summers WK, *et al*. Tacrine as a treatment for Alzheimer's dementia. *N Engl J Med*. 1991: 324; 352.
45. Barar FSK. In: Essentials of Pharmacotherapeutics. S.Chand & Company, New Delhi. 2000: 164-169.
46. Jacob LS. Pharmacology. In: Agents acting on Central Nervous system. 2001:4th edn; 78.
47. Schneider LS. Clinical pharmacology of amino acridines in Alzheimer's disease.*Neurol*. 1993: 43(suppl 4); S64.
48. National Institute for Clinical Excellence. Guidance on the use of donepezil, rivastigmine and galantamine for the treatment of Alzheimer's disease. (www.nice.org.uk/pdf/ ALZHEIMER_full_guidance.pdf.) Issued 20.11.2001.
49. Richard D Howland and Mary J Mycek. In: Lippincott's Pharmacology. 2007: 3rd edn;100-102.
50. Sano M *et al*. A controlled trial of seligiline, α-tocopherol or both as treatment for Alzheimer's disease. *N Engl J Med*. 1997; 36:1216-1222.
51. Tariot PN *et al*, L-phrenyl in Alzheimer's disease. Arch Gen psychiatry. 1987: 44;418.
52. Thompson TL, Morgan MG and Nies AS. Psychotropic drug use in the elderly. (2 parts). *N Engl J Med*. 1983: 308; 134 & 194.
53. www.aarp.org/health/conditions/articles/harvard_a guide-to-alzheimer-s-disease_9.html
54. www.yourtotalhealth.com/html. pp 1-5.
55. A. Elayaraja et al. Nootropic activity of Ethanolic extrat of *Acorus calamus* Linn. *Drug Lines*. 10 (1&2), July 2007 – June 2008, 32-35.
56. R.Lakshmipathy. Health. In: Diet for human brain. 2010. 88(02). 21.