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Alzheimer Disease

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ABSTRACT:-
Alzhermer's disease it is a progressive neurodegerative disease and it is characterized by progressive congnitive deterioration pre-senile and senile dementia are the most common types of Alzheimer's disease. According to world health organization (WHO) survery we found that 5% of men and woman of age above 60 years are most affected the Alzheimer's type demina Clinical manifestation of Alzheimer's disease is characterized by dementia and failure of memory.Presentavailable treatments are acetylcholine inhibitors (rivastigmire,galantamire,derepezil) and D-aspartate receptor antagonist these drugs proved that there is a progression of the disease and relief symptomatically but it is failed to achieve a definite cure.The researcher is found a strong connection between the Alzheimer's and food consume and dementia are similar pathway to cause diabetes 2. That's why then rename Alzheimer is diabetes 3.
KEYWORDS:- Alzheimer, epidemiology, Neurodegeneration, β-amyloid peptide tau protein, pathophysiology, diagnosis, treatment.

I. INTRODUCTION:-

Alzheimer's disease is the most common cause of dementia and it is characterized by a progression form of episodic memory problems.[1] 44 million people of the world-wide population was estimated to the affected by dementia in 2013 and a steep rise to 136 million has will predicted by 2050.[2] There are no treatments with proven disease modifying effects till to date this Alzheimer's disease remains the largest umet medical in neurology. [1]The pathology behind the Alzheimer disease is changes in amyloid precursor protein metabolism, oxidative stress, tau protein phosphorylation impaired energetics, Inflammation mitochondrial, dysfunction, dysregulation of membrane lipid and neurotransmitter pathway disruption.[3] The important factor in Alzheimer's disease is metabolic dysfunction[4] because the pathological features can be directly linked to metabolic abnormalities. For example cognitive dysfunction is occurred due to impaired cerebral glucose uptake and it is an invariant feature of Alzheimer's disease. [5] The pathological events occurs due to neurotoxicity associated with AβH2 causes impaired neuronal energises and leads to the interaction between AβH2 and mitochondrial lead to increased levels of reactive oxygen species (ROS) that affecting glycolysis the TCA cycle and activity of mitochondrial respiratory- chain is accumulation of deleterious intermediate metabolites occurs in the mitochondria.[6] [7]

The recent approaches for the treatment of Alzheimer's disease include the use of some natural products with neuroprotective effects and metabolites to modulate pathways which are associated with neurovascular endothelium through multi-omic analyses.

Alois Alzheimer &AugusleD:-

The great german neuropathologist and psychiatrist Dr. Alosi Alzheimer's describing the dementing condition for the first time and later it is called as Alzheimer's disease. Alzheimer described a case for Auguste D an old women of age 51 years old suffered with a disease of cerebral cortex with progressive memory and language impairment, behavioral symptoms, disorientation and psychosocial impairment. [8]

Epidemiology of Alzheimer'sdisease:-

In united states and many other countries around the world wide this Alzheimer's disease is a critical public health issues and a significant effect on health social and financial burden on society and they estimated that 5million people's of American suffer with Alzheimer's disease and diagnosis are made every 68 seconds the fifth leading cause of death among older elders the major cause is Alzheimer's disease they can estimate that 200 billions are annually spent for individuals suffering with dementia,worldwide we can estimated that people suffering with alzheimer's disease are nearly 35 million people.9

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In 2030 we can estimated that 65 million people have dementia.Alzheimer's disease is a multifactorial and has no single cause to know about the disease there are several modifiable risk factors and associated with development and progression. The greatest risk factor for the development of alzheimers disease is age 10,11

The people who are aged 65 or above 65years are suffering from alzheimers disease
Alzhemers disease is developed by the rare genetic mutations occurred by the older people before age 65 which it is know as early onset or familiar alzhemers disease12,13

If any dominat mutation occurs on autosome eithere one of the presenilin gene located on chromosome 21 it is know as epsilon fourallele of that apolipoprotiean E gene located on chromosome 19 it is the major risk factor for development of spordicalzhemers disease14,15

Pathophysiology:-
The main pathological condition of Alzhemer's disease is the presence of amyloid plaques and neurofibrillary tangles[NFT] it leads to secondary dilation of the ventricles. At hippocampus temporal cortex and nucleus basalis of meyernet more deposists are found it can lead to the reduced levels of neurotransmitter specifically acetylcholine causing congunitive deficits.16

The main pathological cause of Alzheimer's disease is not known and research is ongoing to known the pathological reason for causing Alzheimer's disease the current understanding many hypothesis are come forward for the pathogenesis of Alzheimer's disease.17
Some of them are accepted they are:-

- Amyloid cascade hypothesis
- Tau hypothesis
- Mitochondrial cascade hypothesis

Amyloid cascade hypothesis :-

This is the accepted hypothesis the basic pathology of amyloid cascade hypothesis is deposition of AβH2**.** Amyloid-plaques in the brain and thisAβH2 is derived from amyloid precursor protein (app)by the action of γ secretease and β secretease.18 Plaque is formed by the aggregate of AβH2 and cause oxidative damage and intiates inflammatory process leading to death of a neuron.19,20

In familiar form of Alzheimer's disease is also called early onset and once associated with mutation occurs in Appgene ,pensenillin(chromosome-14) and pensenillin-2 gene all these fragments are come together and mixed with other neuron, non-nerve cells in Alzheimer's disease these develops the plagues in hippocampus areas of cerebreal cortex.
Still we don't know these β-amyloid plagues themselves to cause Alzheimer's disease (or) any product of these β-amyloid plagues can cause the Alzheimer's disease.21

Tau Hypothesis:-

The amyloid cascade hypothesis doesn't explain about the sporadic case of Alzheimer's disease and level of amyloid desposist it lead to the cognitive decline. This can lead to Tau hypothesis which asserts the deposition of Tau and formation of neurofibrilliary tangles is the main pathological reason. Tau is binding to tau microtubules then hyperphospherylated occurs at Tau into neurofibrilliary tangles and reduce the amount of Tau then it is available to bind microtubules.22

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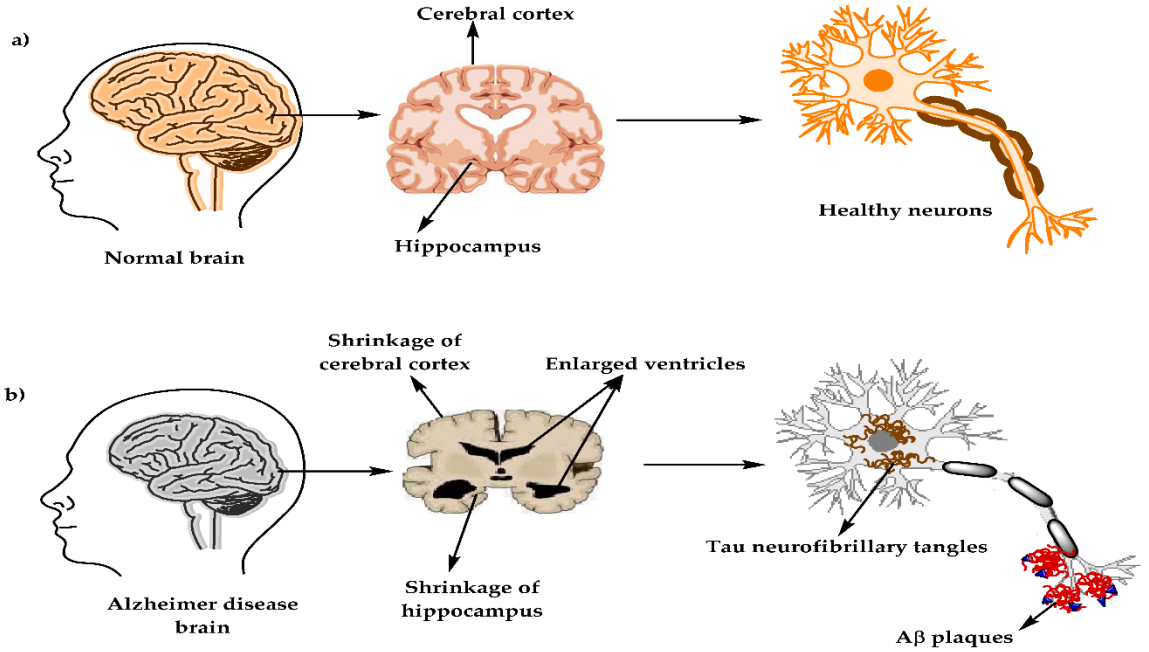

Figure 1
The physiological structure of the brain and neurons in (**a**) healthy brain and (**b**) Alzheimer's disease (AD) brain.

Mitochondrial cascade hypothesis:-
The initating step in Alzheimer's disease is reduced mitochondrial function to handle the free radicals.23

Brain changes associated with A.D

100 billon neurons are present in a healthy adult brain. Each neuron are long and branching extensions these extensions of individual neurons helps to connections with other neurons. Such connections are called "synapse" information flows in a small burts of chemicals that are realised by one of neuron and then detected by other neuron. The normal brain contains 100 trillion synapses.The signals travel rapidly throught the brain's neuronal circuits .It creating the cellular basis of memories, movements, sensation etc..,24

The fragments of protein called as beta-amyloid plagues accumulated at outside the neuron and this accumulation of these abnormal form of the protein is called tau tangles. So by observing theses changes we can conclude that inside neuron there are two of several brain changes associated with Alzheimer's. The accumulation of the plaques and small beta amylodcalled oligomer's24

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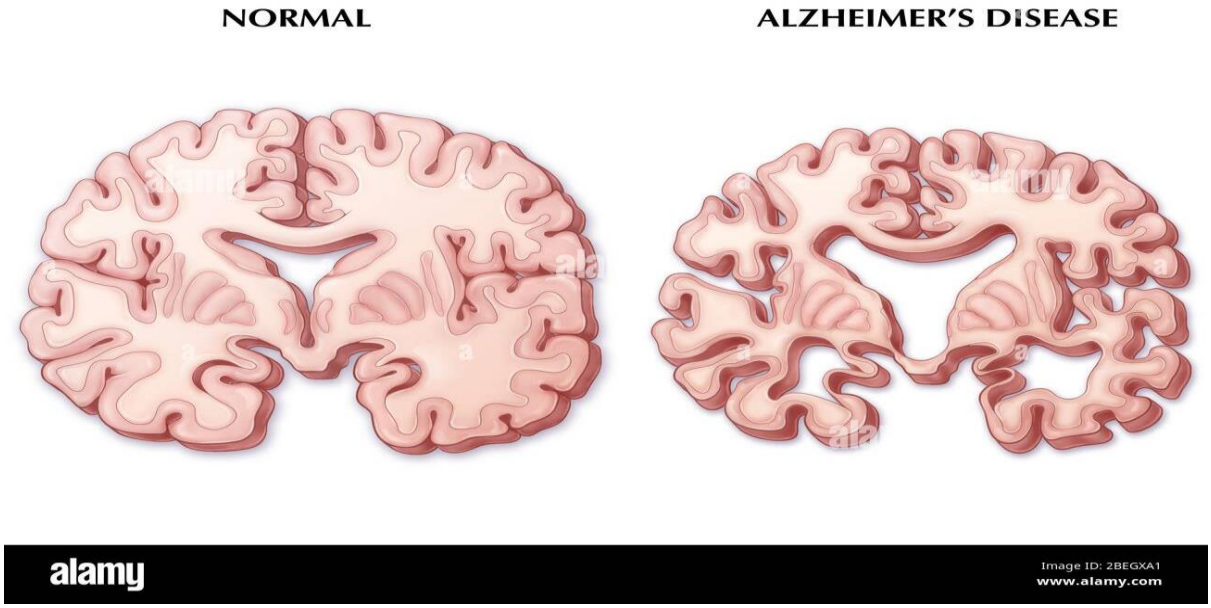

Pharmacological therapy review for Alzheimer's disease :-

The pharmacologic therapy for Alzheimer's disease provides only for short-term improvement for a short period of time i.e., 6 to 8 months.25 In US and several parts of Europe the only medicine approved for those countries are cholinesterase inhibitors and memantine these drugs do not alter the pathology of Alzheimer's disease but the allow the brain to compensate the loss of neurones that communicate via acetylcholine, which acts as a neurotransmitter.26

cholinesterase inhibitors :-

It act by increasing the acetylcholine levels, and it is used by the nerve cells to communicate with each other and it is important factor for memory learning and some congnitive functions for this category. 3 drugs are available donepezil, rivastigmine and galantamine these are used for the treatment of Alzheimer's disease and approved by food and drug administration (FDA).27,28

In all stages of Alzheimer's disease we can use donepezil, galantamine and rivastigmine are used for treatment in mci and dementia stages only galantamine and donepezil are the reversible inhibitors of acetylcholinesterase. Donepezil is used only once- daily dosing and galantamine is used for twice daily as a tablet form (or) as a once- daily extended release in capsule form. If the person has severe liver dysfunction (or) end- stage of renal disease these drugs cannot be used. Rivastigmine is available in transdermal and oral formulation. The common side effect of cholinesterase inhibitors are nausea, vomiting, diarrhea. These due to increased vagaltonebradycardia , cardiac conduction defects can occurs29

Partial N- methyl D – Aspartate (NMDA) Memantine

NMDA antagonist memantine blocks the NMDA receptors and slow the intracellular calcium accumulation it is used to treating moderate to sever A.D and approved by FDA the common side effects are dizziness, bodyache, constipation ,and head ache it can also used in combination with cholineestarases inhibitors 16.30

It is also used to treat anxiety, psychosis and depression which are found in the mild to late stages of A.D avoid tricycleicantideppresants because of their anticholinergic activity

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New medicines under development for A.D

DRUG NAME	COMPANY	INDICATION	DEVELOPMENT STSTUS
ABT-126	Abbot	A.D	Phase-2
ABT-12-Acetyl-cholinesterase	Abbot	A.D	Phase-2
AZD 3480	Targaceptinc	A.D	Phase-2
LY2886721	Elililly& company	A.D	Phase-1
MABT5102A	Genentech	A.D	Phase-2
AVP-923	Avonir-pharmaceuticals	A.D,Mildcongentive impairment	Phase-2
AZD5213	Astrazeneca	A.D	Phase-2
GANTENERUMAB	Hoffmann-la rachea	A.D	Phase-3
GSK2647544	Glaxosmithkline	A.D	Phase-1
B11B037	Biogen Idec	A.D Partial or mild A.D	Phase-1
BMS-241027	Bristol-Myerssquibb	A.D	Phase-1
AAB-003	Pfizer	A.D	Phase-1

NON-PHARMACOLOGICALTherapy:-

Non Pharmacological therapy does not involvemedication the main goal of non pharmacology therapy of A.D is maintaining or Improving congentive function overall quality of life and reducing behavioral symptoms such as apathy, disturbances and aggression31

A recent analysis is done for pharmacologoical treatment for agitation and aggression in people with dementia. It concluded that non-pharmacological interventions which reduces the aggression and agitation some examples of non-pharmacological therapies include computerized memory training, using special lighting to lessen sleep disorders and to listening to favorite music as a way to recall. These pharmacologic therapies dose not stop or slow down the damage and destruction of neurons that cause alzheimers symptoms32,33

It is difficult to know the effectiveness of non-pharmacological therapies because of the large number of unique therapies are tested the lack of standard method for carrying out any individual therapy. So based on these multiple factors it is challenging to group together and compare those with non-pharmacological therapies34

Researchers have done multiple studies of non-pharmacologic therapies to provide insight into their potential effectiveness .A meta analysis concluded of aerobic exercise and a combination of aerobic and non aerobic exercise had a positive effects on cognitive function in people with A.D

Another systematic review that cognitive stimulation had benefical effects on cognitive

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stimulation had beneficial effects on cognitive function with people leaved in Alzheimer's dementiaanother review that cognitive stimulation is music based therapie and psychological treatment35,36

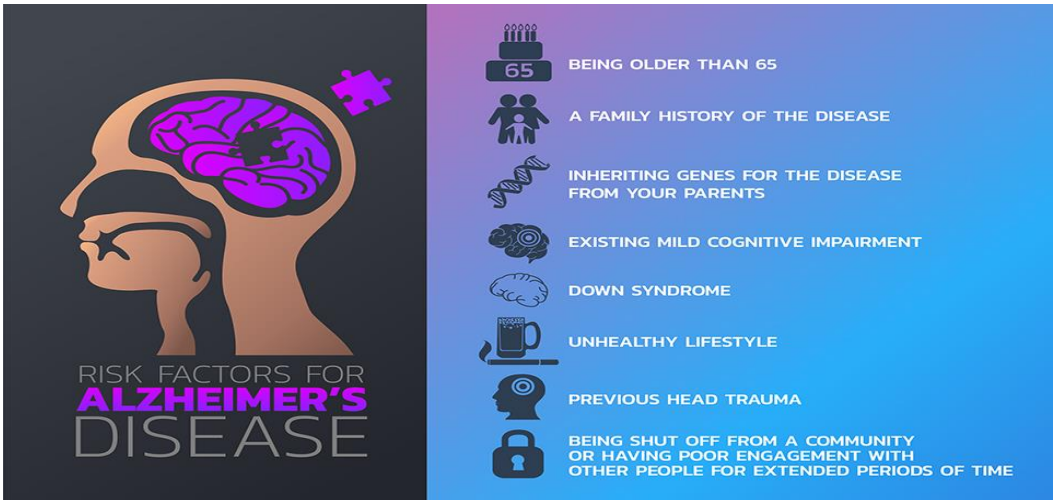
Causes of disease:-

Alzheimer's disease deteriorate of brain cells causes the lose connections with each other and eventually die. These changes area associated with accumulation of abnormal proteins that form plaques and tangles in brain cell.

Scientist believe that combination of lifestyle, environmental and genetic risk factor trigger the abnormal biological process in brain that results in Alzheimer's disease.

Some risk factors include:-

- Increasing age
- Down syndrome
- Family history
- Lack of regular exercise
- History of a head injury
- Poor sleep habits
- High blood pressure
- High blood cholesterol
- Obesity
- Poorly controlled type 2diabetes etc



Diagnosis:-

There are no accurate diagnostic methods for Alzheimer's disease. The early diagnosis was very important since it is stage when the pharmacological therapy will be successful to treate reversible diseases currently the definition of the gray zone between mild dementia and aging is high priority. This state is called mild cognitive impairment (MCI)

The mild cognitive impairment include:-

- Normal daily activities
- Abnormal memory of the age
- Absence of derrentia
- Memory complaints
- Other cognitive functions are actually normal36.

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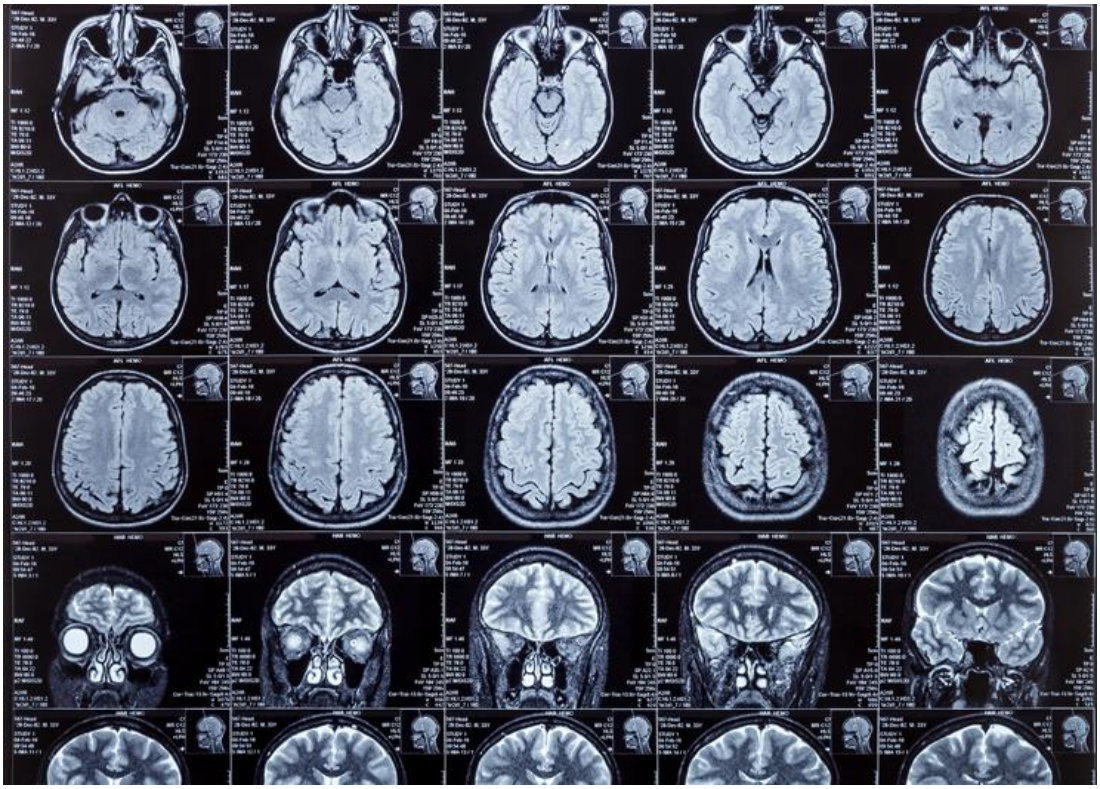

Alzheimer's and diabetes:-

There are certain disease that connected to our diet like diabetes the researchers are found a consume and dementia are similar pathway to cause diabetes2, that's why they rename Alzheimer's is diabetes 3. In Alzheimer's disease the brain glucose metabolism level are deteriorated. According to research type 2 diabetes mellitus are increase the risk of Alzheimer's disease.37

The studies show that increase glucogon like peptide helps to normalize insulin signalling in diabetes type 2. This glucogon like peptide is involved majority in activities in brain functions. Animal study researchers Alzheimer is a charactersties in interfering the insulin signal in brain.38

Alzheimer's disease and diabetes are linked together because insulin resistance and diabetes are both increased the development of plagues in brain.38

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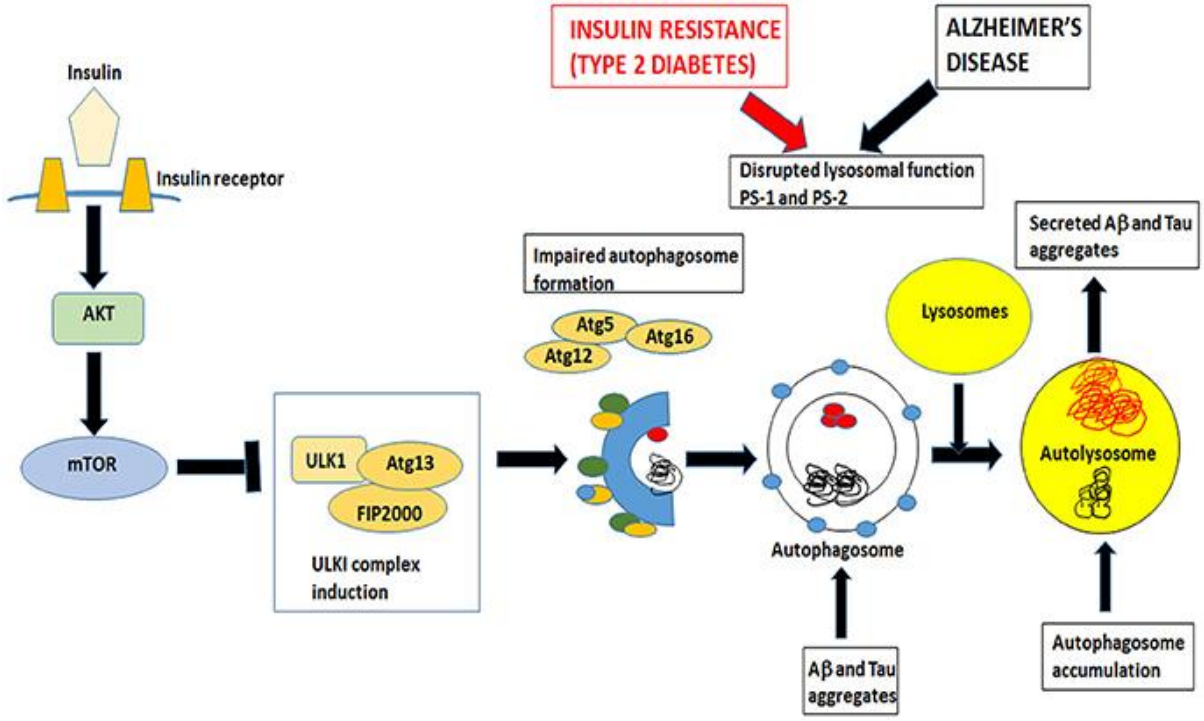

Invitro models of A.D:-

Invitro models of A.D allow study of any changes in pathological and cellular level. These models have stricty controlled all conditions and lower costs a simpler maintenance and handling when compared to invivo models.39.40 These studies can be carried out with preliminary efficacy and with shorter time scales with pharmacodynamic experiments can be carried out 0f cell models.for the report purpose we use invitro models like 2-D &3-D cell culture and included pluripotent stem cells (ipscs) using tissue models and primary cultures will also used.41,42

MODEL		PATHOLOGICAL RELEVANCE TO A.D	PHENOTYPE & ASSESMENT	ADVANTAGE	DISADVANTAGE
2D cell culture	HBMEC	Barrier property like BBB	Study drug delivery	Inexpensive	Not representative of real environment
	BCEC	Retain BBB characteristics	Study drug delivery	Inexpensive	Not representative of real environment

REFERENCES :-

[1]. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, et al. (2013) The global prevalence of dementia: A systematic review and metaanalysis. Alzheimers Dement 9: 63.e2-75.e2.

[2]. Gilman S (2010) Oxford American handbook of neurology. Oxford University Press, Oxford, UK.

[3]. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, et al. (2007) Prevalence of dementia in the United States: The aging, demographics, and memory study. Neuroepidemiology 29: 125-132.

[4]. Ott A, Breteler MM, van Harskamp F, Claus JJ, van der Cammen TJ, et al. (1995) Prevalence of alzheimer's disease and vascular dementia: Association with education. The Rotterdam study. BMJ 310: 970-973.

[5]. Querfurth HW, LaFerla FM (2010) Alzheimer's disease. N Engl J Med 362: 329-344.

[6]. Selkoe DJ (2002) Alzheimer's disease is a synaptic failure. Science 298: 789-791.

[7]. Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, et al. (2005) Correlations between apolipoprotein E epsilon4 gene

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dose and brain-imaging measurements of regional hypometabolism. Proc Natl Acad Sci U S A 102: 8299-8302.

[8]. Sommer I, Griebler U, Kien C, Auer S, Klerings I, et al. (2017) Vitamin D deficiency as a risk factor for dementia: A systematic review and meta-analysis. BMC Geriatr 17: 16.

[9]. Abidar, S., Boiangiu, R. S., Dumitru, G., Todirascu-Ciornea, E., Amakran, A., Cioanca, O., et al. (2020). The Aqueous Extract from Ceratonia Siliqua Leaves Protects against 6-hydroxydopamine in Zebrafish: Understanding the Underlying Mechanism. Antioxidants (Basel) 9, 1–21. doi:10.3390/antiox9040304

[10]. Aevarsson O, Skoog I 1996. A population-based study on the incidence of dementia disorders between 85 and 88 years of age. J Am Geriatr Soc 44: 1455–1460 [PubMed] [Google Scholar]

[11]. Aisen PS, Cummings JL, Schneider LS 2011. Symptomatic and non-amyloid/Tau-based pharmacologic treatment for Alzheimer disease. Cold Spring Harb Perspect Med 10.1101/cshperspect.a006395 [PMC free article] [PubMed] [Google Scholar]

[12]. Akbaraly TN, Portet F, Fustinoni S, Dartigues JF, Artero S, Rouaud O, Touchon J, Ritchie K, Berr C 2009. Leisure activities and the risk of dementia in the elderly: results from the Three-City Study. Neurology 73: 854–861 [PubMed] [Google Scholar]

[13]. Andersen K, Nielsen H, Lolk A, Andersen J, Becker I, Kragh-Sorensen P 1999. Incidence of very mild to severe dementia and Alzheimer's disease in Denmark: The Odense Study. Neurology 52: 85–90 [PubMed] [Google Scholar]

[14]. Angevaren M, Aufdemkampe G, Verhaar H, Aleman A, Vanhees L 2008. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. Cochrane Database of Systematic Reviews (Online): CD005381 [PubMed] [Google Scholar]

[15]. Arbus C, Soto ME, Andrieu S, Nourhashemi F, Camus V, Schmitt L, Vellas B 2008. The prevalence of clinically significant depressive symptoms in Alzheimer's disease: relationship with other psychological and behavioural symptoms. Int J GeriatrPsychiat 23: 1209–1211 [PubMed] [Google Scholar]

[16]. 16.J. Ramirez-Bermudez Alzheimer's disease: critical notes on the history of a medical concept Arch Med Res (2012)

[17]. D.S. Auld et al. Alzheimer's disease and the basal forebrain cholinergic system: relations to β-amyloid peptides, cognition, and treatment strategies Prog Neurobiol (2002)

[18]. A. Kurz et al. Novel insights for the treatment of Alzheimer's disease Prog NeuropsychopharmacolBiol Psychiatry (2011)

[19]. D. Galimberti et al. Immunotherapy against amyloid pathology in Alzheimer's disease J Neurol Sci (2013)

[20]. Y. Xu et al.Neurotransmitter receptors and cognitive dysfunction in Alzheimer's disease and Parkinson's disease Prog Neurobiol (2012)

[21]. K. Yasojima et al.Relationship between beta amyloid peptide generating molecules and neprilysin in Alzheimer disease and normal brain Brain Res (2001)

[22]. E.E. Tuppo et al.The role of inflammation in Alzheimer's disease Int J Biochem Cell Biol (2005)

[23]. G. Silvestrelli et al.Treatment of Alzheimer's disease: from pharmacology to a better understanding of disease pathophysiology Mech Ageing Dev (2006)

[24]. L. Buée et al.Tau protein isoforms, phosphorylation and role in neurodegenerative disorders Brain Res Rev (2000)

[25]. Aisen PS, Davis KL, Berg JD, et al. A randomized controlled trial of prednisone in Alzheimer's disease. Neurology. 2000;**54**:588–93. [PubMed] [Google Scholar]

[26]. Aisen PS, Schafer KA, Grundman M, et al. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA. 2003;**289**:2819–26. [PubMed] [Google Scholar]

[27]. Almeida OP, Flicker L. Testosterone and dementia: too much ado about too little data. J Br Menopause Soc. 2003;**9**:107–10. [PubMed] [Google Scholar]

[28]. Anonymous NICE faces legal challenge over restriction on dementia drugs. BMJ. 2006;**333**:1085. [PMC free article] [PubMed] [Google Scholar]

[29]. Auriacombe S, Pere JJ, Loria-Kanza Y, et al. Efficacy and safety of rivastigmine in patients

International Journal of Pharmaceutical research and Applications
Volume 8, Issue 4, Jul.-Aug. 2023, pp: 1682-1691 www.ijprajournal.com ISSN: 2456-4494

with Alzheimer's disease who failed to benefit from treatment with donepezil. Curr Med Res Opin. 2002;**18**:129–38. [PubMed] [Google Scholar]

[30]. Balk EM, Raman G, Tatsioni A, et al. Vitamin B6, B12, and folic acid supplementation and cognitive function: a systematic review of randomized trials. Arch Intern Med. 2007;**167**:21–30. [PubMed] [Google Scholar]

[31]. Bartorelli L, Giraldi C, Saccardo M, et al. Effects of switching from an AChE inhibitor to a dual AChE-BuChE inhibitor in patients with Alzheimer's disease. Curr Med Res Opin. 2005;**21**:1809–18. [PubMed] [Google Scholar]

[32]. Bent S, Goldberg H, Padula A, et al. Spontaneous bleeding associated with Ginkgo biloba – a case report and systematic review of the literature. J Gen Intern Med. 2005;**20**:657–61. [PMC free article] [PubMed] [Google Scholar]

[33]. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006;(1):CD005593. [PMC free article] [PubMed] [Google Scholar]

[34]. Birks J, Grimley Evans J, Iakovidou V, et al. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev. 2000;(4):CD001191. [PubMed] [Google Scholar]

[35]. Birks J, Grinley EV, Van Dongen M. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev. 2002;(4):CD003120. [PubMed] [Google Scholar]

[36]. Birks J, Harvey R. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev. 2006;(1):CD001190. [PubMed] [Google Scholar]

[37]. Abbas T, Faivre E, Holscher C (2009) Impairment of synaptic plasticity and memory formation in GLP-1 receptor KO mice: Interaction between type 2 diabetes and alzheimer's disease. Behav Brain Res 205: 265-271.

[38]. Agrawal R, Gomez-Pinilla F (2012) Metabolic syndrome' in the brain: Deficiency in omega-3 fatty acid exacerbates dysfunctions in insulin receptor signalling and cognition. J Physiol 590: 2485-2499.

[39]. Agholme, L., Lindstrom, T., Kagedal, K., Marcusson, J., and Hallbeck, M. (2010). An in vitro model for neuroscience: differentiation of SH-SY5Y cells into cells with morphological and biochemical characteristics of mature neurons. J. Alzheimers Dis. 20, 1069–1082. doi: 10.3233/JAD-2010-091363

[40]. Ahn, S. I., Sei, Y. J., Park, H. J., Kim, J., Ryu, Y., Choi, J. J., et al. (2020). Microengineered human blood-brain barrier platform for understanding nanoparticle transport mechanisms. Nat. Commun. 11:175. doi: 10.1038/s41467-019-13896-7

[41]. Almeida, S., Zhang, Z., Coppola, G., Mao, W., Futai, K., Karydas, A., et al. (2012). Induced pluripotent stem cell models of progranulin-deficient frontotemporal dementia uncover specific reversible neuronal defects. Cell Rep. 2, 789–798. doi: 10.1016/j.celrep.2012.09.007

[42]. An, M. C., Zhang, N., Scott, G., Montoro, D., Wittkop, T., Mooney, S., et al. (2012). Genetic correction of Huntington's disease phenotypes in induced pluripotent stem cells. Cell Stem Cell 11, 253–263. doi: 10.1016/j.stem.2012.04.026