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RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF ALZHEIMER'S DISEASE

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Abstract
An attempt that has continuously expanded over the past ten years has been made to recognize or determine the origin of this disease and to develop pharmacological remedies. Recent advances include enhanced clinical diagnostic criteria and treatment of behavioral and cognitive disorders. Clinically testing a symptomatic treatment that mainly focuses on cholinergic treatment has used randomized, dual, placebo-controlled, parallel-group trials investigating performance-based measures of cognitive performance, tasks of daily life, and behavior. Drugs, such as donepezil, rivastigmine, tacrine, and galantamine, are suggested for patients with Alzheimer's disorder to treat their cognitive deficits. This review emphasized on various recent advancements in terms of treatment , diagnosis and various therapeutic agents which are discussed in use of Alzheimer disease. This review is beneficial for researcher who is doing work on neuroprotective studies.
Key points: *Alzheimer's disease*, *Diagnosis*, *etiology*, *genetics*, *epidemiology*, *Pathophysiology* Diagnosis, *Treatment*,

1. Introduction of alzheimer's disease :-

Alzheimer's disease is one of the most severe brain disorders affecting elderly individuals. An illness that is both undertreated and underrecognized is becoming a substantial public health concern. Alzheimer's disease (AD) has become a significant public health concern due to the general population's higher life expectancy and a better knowledge of the socioeconomic impacts of the condition. In addition, Alzheimer's was first recognized in 1906 using the criteria of progressive memory loss, disorientation, and clinical symptoms. (Senile plaques and neurofibrillary tangles).

Initially assumed to be an uncommon condition, AD was subsequently found to be an inevitable side effect of ageing. Early identification and treatment of AD patients were hampered by ageing stigma and other issues, but these misconceptions are fading, and treatments—even if they were at first ineffective—are increasingly becoming available **(**Sharma, R., Kuca, K., et al., 2019)

2..PATHOPHYSIOLOGY OF ALZHEIMER DISEASE

Cognitive impairment in AD patients is directly linked to synaptic loss in the neocortex and limbic system, among other neuropathological characteristics of AD ([APP (Selkoe, D.J., 1989; Sisodia, S.S. and Price, D.L., 1995; Tanzi, R.E., Gusella, J.F., et al., 1987)], The idea that the pathophysiology of AD is connected to the increasing buildup of amyloid-b (Ab) protein, which is produced by the proteolysis of Ab precursor proteinDeKosky, S.T., Scheff, S.W. and Styren, S.D., 1996). DeKosky, S.T. and Scheff, S.W., 1990) (Wen, P.H., Hof, P.R., et al., 2004;), is supported by a number of lines of research.

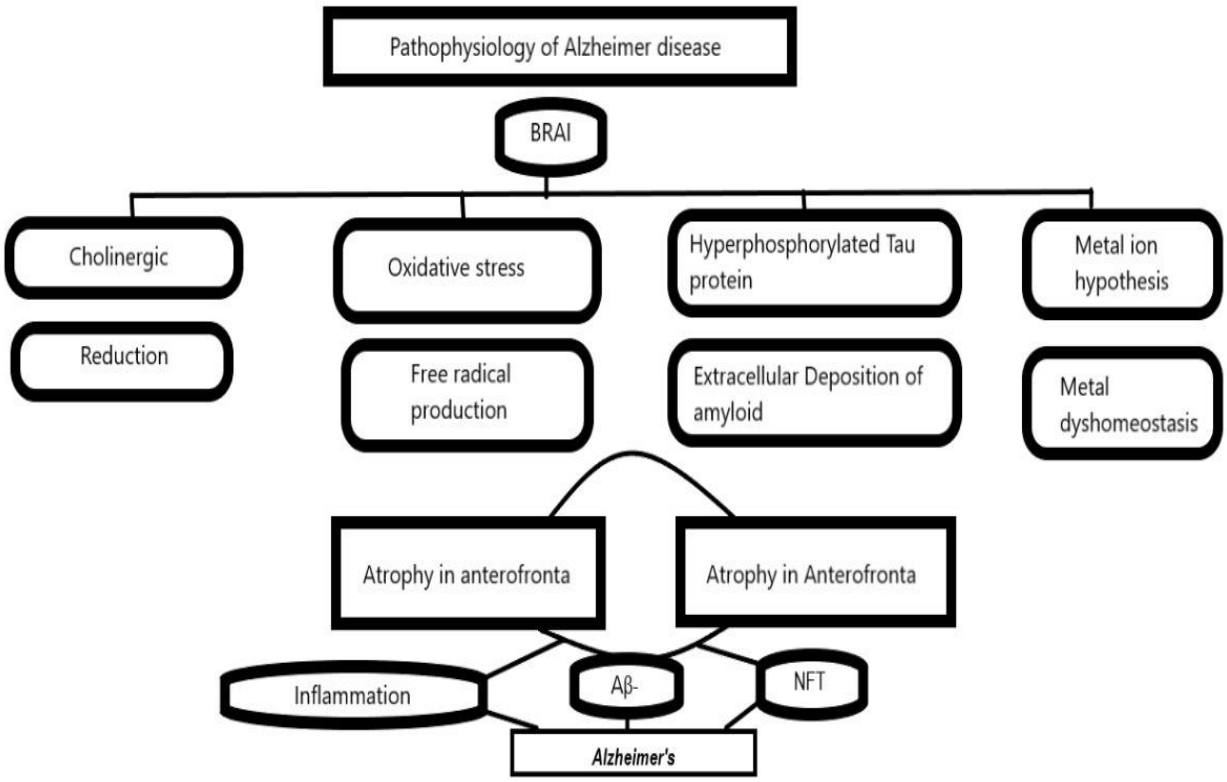

Figure 1: Pathophysiology of Alzheimer's disease

In AD, dementia is linked to neurodegeneration, which is first characterised by synaptic damage Wen, P.H., Hof, P.R., et al., 2004; Chevallier, N.L., Soriano, S., et al., 2005; Donovan, M.H., Yazdani, U., et al., 2006; Jin, K., Galvan, V., et al., 2004; Dong, H., Goico, B., et al., 2004)and then by neuronal death (Terry, R.D., Peck, A., et al., 1981). Iqbal, K. and Grundke-Iqbal, I., 2002; Mandelkow, E.M. and Mandelkow, E., 1998) are all associated with this. More recent research has shown evidence that suggests interfering with adult neurogenesis in the hippocampus may be another factor contributing to AD's neurodegenerative process (Boekhoorn, K., Joels, M. and Lucassen, P.J., 2006; Li, B., Yamamori, H., et al., 2008). Previous research has demonstrated significant modifications in the hippocampus's adult neurogenesis process in transgenic (tg) animal models of AD (Terry, R.D., Masliah, E. and Hansen, L.A., 1994; Masliah, E., Mallory, M., et al., 1997; DeKosky, S.T. and Scheff, S.W., 1990) (Wen, P.H., Hof, P.R., et al., 2004;)[APP (Selkoe, D.J., 1989; Sisodia, S.S. and Price, D.L., 1995; Tanzi, R.E., Gusella, J.F., et al., 1987)]

3.Molecular mechanism of alzheimer's disease:-

The amyloid precursor protein (APP), a member of the type 1 transmembrane family of glycoproteins, is extensively expressed in a range of cell types. According to . Lemaire, H.G., et al., 1987; Kang, J. , the N-terminal region of APP is either localised in the lumen of intracellular vesicles such the endoplasmic reticulum, Golgi apparatus, and intracellular endosomes, or it is ejected towards the extracellular domain. The APP C-terminal region, on the other hand, is located in the cytoplasmic domain. A group of proteases known as, or secretases can degrade APP by performing proteolysis on it. A (1-40) peptide or its A (1-42) version, which has a substantially larger ability for self-aggregation, are produced by secretases (17,18). Secretases normally release A fragments and the extracellular moiety of APP's remaining polypeptide, sAPP, which comes from neurons. (Chen (2000),Neve, R.L., McPhie)

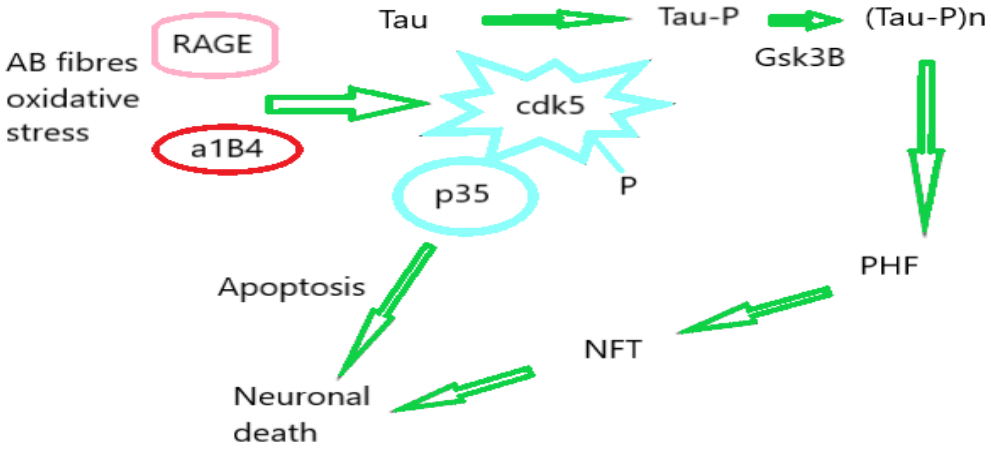

Figure no:-2 Molecular mechanism of Alzheimer's disease.

The hippocampus, entorhinal cortex, and amygdala are the principal locations of neurofibrillary tangles (NFTs) made up of arrays of PHFs. PHFs are abnormal structures formed when hyperphosphorylated versions of tau protein self-assemble into a dense filamentous network. Tau is a versatile microtubule-associated protein that is essential for microtubule building, dynamic instability protection, and connecting these polymers to other cytoskeletal filaments.

Human acetylcholinesterase (AChE) is a crucial enzyme in neural signalling because it breaks down acetylcholine (ACh), which therefore prevents postsynaptic signal transmission (Singh, S.P. and Gupta, D., 2017). In the central nervous system, cholinergic neurotransmission is crucial for neuronal plasticity and cell survival. The intracellular signalling induced by muscarinic (mAChRs) and nicotinic (nAChRs) AChRs (Figure 1) is mediated by G-protein activity and ion flow, respectively (Fukunaga, K. and Yabuki, Y., 2018). ACh is taken up by a unique transport mechanism in the human brain that functions differently pharmacologically from the known organic cation transporters (Muramatsu, I., Yoshiki, H., et al., 2016).

At physiological quantities, A1-42 and A1-16 cause synapsin 1 to become dephosphorylated. This causes calcineurin to become activated, which expands the synaptic vesicles (SV) circulating pool. The presynaptic release of neurotransmitters is increased during this phase, which improves neuroplasticity and memory formation (Anni, D., Weiss, E.M., et al., 2021).

Diagnosiof Alzheimer's disease: -

The Clinical manifestationsof AD include difficulties with language and memory, visual perceptual direction, and superior executive function. Personality changes, impaired judgment, wandering, psychosis, mood disorder, agitation, and irregular sleep patterns are examples of non-cognitive alterations ((Kosik, K.S., and Mandelkow, E.M., Biernat, J., et al., 1995;Cross, D., Vial, C. and Maccioni, R.B., 1993; Saragoni, L., Hernández, P. and Maccioni, R.B., 2000).

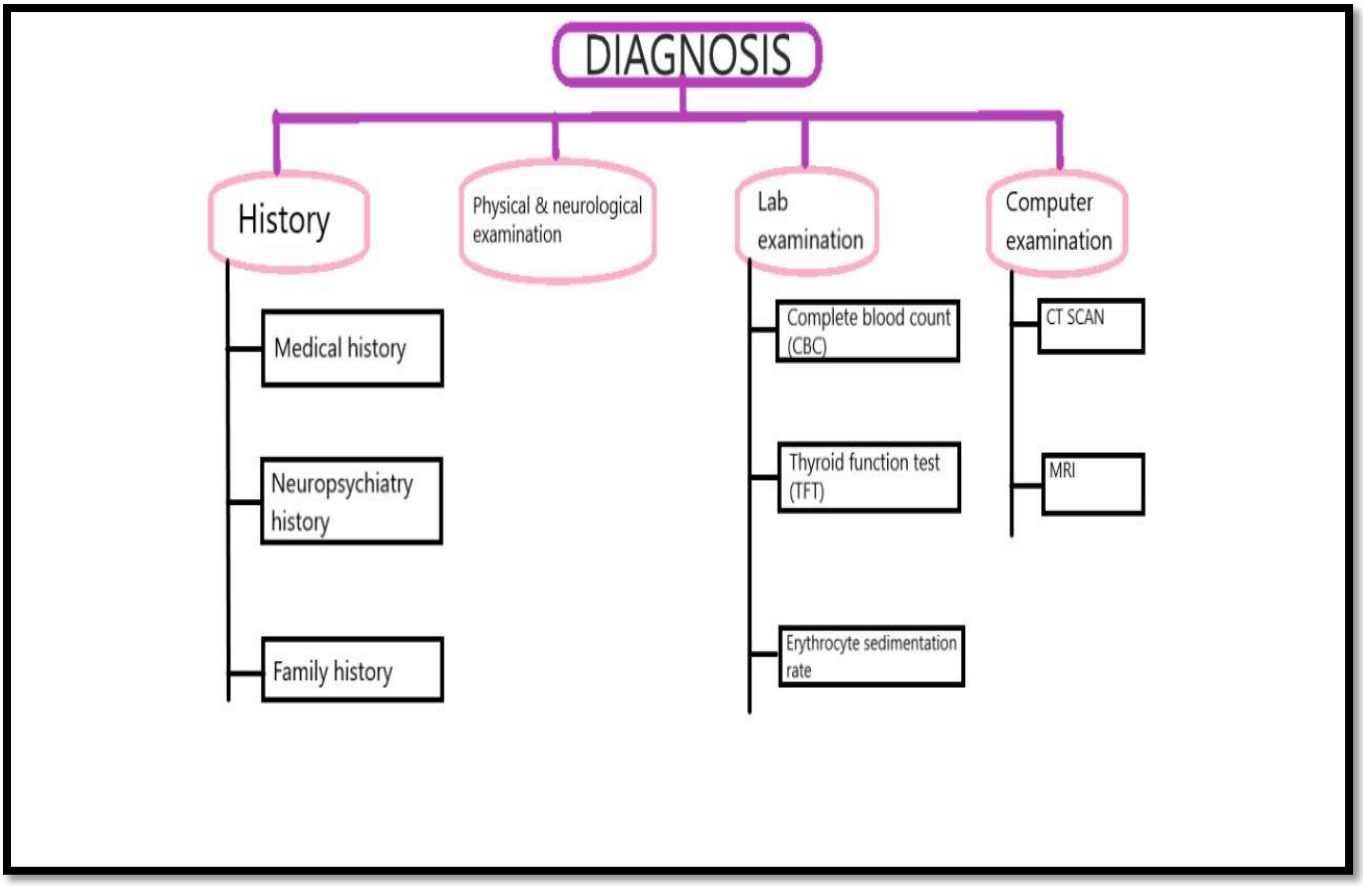

Figure 3: Diagnosis of Alzheimer's disease

Difference between normal brain and AD brain

Before becoming silent and immobile, patients often encounter gait and motor difficulties in the latter stages. Patients with AD generally live for 8 to 10 years following their diagnosis, even though the condition might last up to 20 years (Näslund, J., Haroutunian, V., et al., 2000)

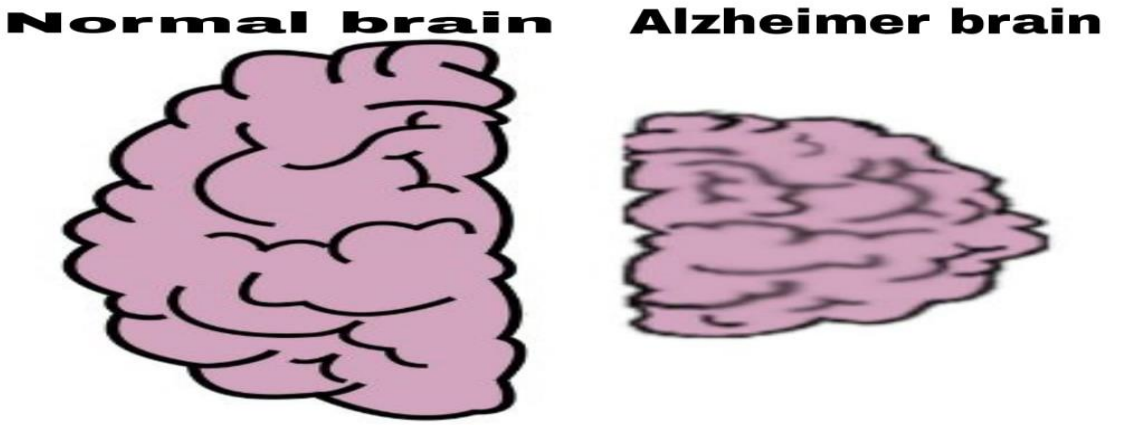

Figure4 :- Pictorial Representation of Normal Brain and Alzheimer's Brain

Etiology of Alzheimer's disease

Senile plaque and neurofibrillary tangles appear to be the primary in neuropathological signs of AD. As the illness advances, it appears that senile plaque production starts in brain areas connected to cognition before spreading to other cortical areas. The (A), a piece of the amyloid precursor, is one of the components of senile plaques (APP). The creation of a peptide from APP occurs as a result of two subsequent cleavage events: -secretes generates one end of the peptides by proteolytic enzymes activity, and -secretes generates the other end through the same mechanism. The shorter A40 and the lengthier A42 appear to be 2 distinct varieties of A. A42 appears to have been implanted first and could have played role in the chain of events. Finally, beta protein deposition results. It is currently unclear if senile plaque are the cause of the condition or a consequence of the dysfunctional APP metabolism, which raises the levels of insoluble A. By inducing inflammation or an increase in free radical generation, for example, A seems to be toxic to neurons either directly or indirectly (Mooser, V., Helbecque, N., et al., 2000) The togethereing of neurofibrillary is another feature of AD. The chemically altered (misfolded proteins and phosphorylated) neurofibrillary tangles are predominantly caused by tau protein, which involved in the production of microtubules. The severity of the disease correlates with an increase in the amount of tau tangles in the brain; Although some families with that mutation have been recognized as having front temporal dementias with Parkinsonism, there haven't been any cases of AD a result of a tau gene mutation on chromosome 17 (Launer, L.J.,Andersen, K., et al., 1999**)**

Recent research supports the notion that tau alterations follow An accumulation in AD patients .

Genetics

The best support for amyloid's fundamental involvement in AD came from our understanding of the likely procedures for every one of the four identified genes that cause family illness variations.

There are 3 particular gene variants (On chromosome 21 APP, On chromosomes 14 presenilin-1 [PS 1], and On chromosome 1 presenilin-2 [PS 2]) were found to be present in patients but they are incredibly uncommon—they account for less than 1% of cases. All of these genes seem to encourage the cleavage of APP by either - or -secretive, which in turn seems to improve cellular synthesis of A-42. Numerous studies have found a dose-dependent relationship between the

APOE-4 allele and individuals with early-onset AD as well as an increased risk for AD. But some research suggests that the APOE-2 allele can be advantageous. 1 or 2 two copies of the APOE-4 allele on human chromosome seem to increase the likelihood of the sporadic late-onset variant of Alzheimer's disease. Only a risk factor, APOE-4 is not essential nor enough to cause AD. An estimated 45%–60% hereditary risk with APOE-4. Instead of raising A's production, APOE-4 seems to act by clearance. Lipoprotein(a), a recently discovered potential risk factor, appears to both increase the incidence of delayed AD in persons with the APOE-4 allele and to protect against it in individuals who aren't carriers (Launer LJ, Andersen K, et al., 1999**)**

Women Having a greater risk of AD than males, while being equally susceptible to vascular dementia, according to a number of retrospective studies that were conducted as projects. Only in part because of their longer lifespans, women seem to have a larger risk of developing AD. Women who have AD because they live longer than males with the condition. These studies also revealed that although a history of head trauma with unconsciousness and a family history of dementia did not significantly increase the risk of AD, low levels of education did(Hendrie,.Gao, S., and Hui, S., 1998; American Psychiatric Association, 1997).

1. Management and Treatment of AD

1.1.Psychosocial treatment

Patients with AD can function better when their environment is altered, their families are supportive, and other medical comorbidities are avoided. A patient's surroundings need to be adjusted in order to keep As long as AD sufferers remain in their homes, feasibly. Written daily reminders might be useful for carrying out everyday tasks. It's crucial to have visible clocks, calendars, and windows. Activities performed by patients should not alter much. It's crucial to maintain a healthy diet, regular exercise, and hygiene. Since family members are susceptible to depression, anxiety disorders, and insomnia, family support is crucial **(**Schachter AS, Davis KL., 2000; Schachter, A.S. and Davis, K.L., 1999**)**

1.2. Pharmacotherapy

Cognitive enhancers are among the current pharmaceutical options available to clinicians treating AD for the management of the cognitive deficiency **(**Friedhoff, L.T.,Rogers, S.L and Donepezil Study Group, et al., 1998**).**As well as psychiatric medications, mood stabilizers, antidepressants, and hypnotics to treat behavioural issues**.** (Schachter, A.S. and Davis, K.L., 1999)

Cholinesterase inhibitor

The cholinergic deficit seen in AD is the basis for the utilization of cholinesterase inhibitors. For AD patients, only cholinesterase inhibitors have demonstrated clinically significant results. By preventing the hydrolysis-related enzymes, these substances enhance the amount of acetylcholine that is accessible for synaptic transmission (ie, acetylcholinesterase). These medications seem to be helpful throughout the course of the illness, but especially in the medial stage **(**Uchida, K.M.,and Shintani, E.Y. 1997)

TABLE1: Cholinesterase inhibitor

Drug Name	Dosage	Side effects
Donepezil	**5-10mg qhs**	**Loss of appetite, weight loss**
Galanthamine	**5-12 mg bid**	**Frequent urination, Muscle cramps**
Tacrine	**20-40 mg qid**	**Convulsion, Seizure**
Rivastigamine	**6-12mg bd**	**Diarrhea, muscle cramps**

1.2.1. Estrogen replacement therapy

Numerous Studies have looked at how oestrogen affects the development of the brain., neuronal survival, repair, and plasticity. Through enhancing transcription and modulating non-genomic events, it appears to function in the brain. The capacity of the brain to aromatize testosterone gives males an internal source of estrogen, whereas postmenopausal women experience a dramatic drop in estrogen production that increases their risk of developing AD. There is accumulating evidence from
several open-label clinical trials suggesting estrogen replacement therapy (ERT) in postmenopausal women**(**Cotman, C.W.,Mulnard, R.A., et al., 2000**)** In addition to at least one double-blind, placebo-controlled research. Ignoring the fact that a recent, sizable, double-blind, controlled.(Paganini-Hill A,Henderson VW et al., 1994; and Craft, S., et al., 1999**).**experiment found no evidence of an estrogen impact in AD patients. In one of the latter studies, estrogen gave a brief (2-month) benefit on the MMSE, but after a year of use, it had no effect on cognitive or functional result**s (**V.W., Paganini-Hill, A.,Henderson, et al., 2000; W.F., Kawas, C.,Stewart et al., 1997**).**

1.2.2. Anti-inflammatory agents

Some retrospective epidemiologic investigations have provided evidence in favour of the idea that anti-inflammatory medication can decrease AD development **(**Kirby, L.C., Rogers, J et al., Veld BA., Launer LJ., et al., 1998;1993Gau, B.A.,Breitner, J.C.S et al., 1994;**).** (NSAIDS) prospective double-blind clinical studies in AD are quite rare. NSAIDS such as Indomethacin **(**Scharf, S., et al., 1999**),** ibuprofen **(**Aisen, P., et al., 1996**),** diclofenac **(**Davis, K.L.,Aisen, P.S.,et al., 2000**),** and naproxen with non-randomized research. Prednisone at a modest dose **(**Aisen, P.S., Davis, K.L., et al., 2000**)** and other anti-inflammatory drugs showed promising results in slowing the course of the disease. Unfortunately, this research only employed small sample sizes. The earlier encouraging findings have not been confirmed by more recent investigations. In 138 AD patients participating in a 16-month, dual, placebo-controlled, less-dose research, steroids don't reduce the pace of cognitive deteriorate when compared to the control group **(**Altsteil L., Marin D.,Aisen PS., et al. 1995**).** Although some earlier high-dose prednisone studies indicated benefit, using high-dose steroids repeatedly can result in serious health issues**. (**Thai L., 2000**)** Cyclooxygenase-2 (COX-2) inhibitors are a different family of anti-inflammatory drugs (celecoxib, rofecoxib). Due to their greater attention to the mind than the presently available NSAIDs, they are increasingly recommended in clinical trials for AD patients. The outcome of a significant dual -controlled blind placebo experiment contrast rofecoxib with naproxen and placebo was unfavourable. (Riekkinen, P.J., 1998**)**

Table 2: ***Anti-inflammatory agents***

DRUG CLASS	**EXAMPLE**
NSAID'S	Ibuprofen,Diclofenac,Naproxene
Low dose steroids	Prednisone
Anti-inflammation medication	HCQ,Colchicine
Cox-2 inhibitors	Celecoxib, rofecoxib

1.2.3. ANTI-OXIDATIVE AGENTS

According to current views, increment in Free radical production may contribute to AD. which would have a direct harmful impact. Catecholamine's are present, and there is just a little amount

of antioxidant enzymes in the brain may make it susceptible to the harmful effects of oxidative stress. A has also been linked to an increase in free-radical production.

Selegiline, a monoamine oxidase B antagonist, is taken orally once a day in dosages of 5 to 10 mg. and 1000 IU of vitamin E twice daily **(**P.N Tariot, et al., 1998; Filip, V. and Kolibas, E., 1999; Ernesto, C.,Sano, M et al., 1997**),** serve as free-radical decomposers to lessen damage caused by free radicals**,** Recent significant double-blind research**. (**Amin, M., Nair, N.P.V et al.,1995**)**

Table 3. Common Treatment of AD

Anti-Depreesent	**Anti-Psychotics**
Fluoxetene	Risperidone
Paroxetene	Olanzapine
Fluvoxamine	
Citalopram	

Treatment for both the cognitive and behavioural issues seem to postpone nursing home admission and increase morbidity and mortality, which has a serious financial effect on AD **(**Taragano, F.E., et al., 1997; Katona, C.L., et al., 1998**)**

2. Therapeutic potential of phytoconstituents in AD

The therapy of Alzheimer's disorder and memory impairment involves the utilization of medicinal herbs in a substantial way. Ayurveda, homoeopathic, unani, and siddha systems of medicine are among the most significant traditional therapeutic modalities. Because the medicine system of unani typically gives a extremely scientific kind of healthcare as like a heavenly gift, the medical community is increasingly interested in medicinal plants. Fundamentally, the traditional medical system is preventative, protecting, nourishing, and curative. Traditional medicines treat patients safely and effectively while having little to no negative effects.

Ancient societies including Egyptian, Indian, and Chinese ones are where herbal remedies first appeared. It improves overall health and wellbeing and uses medicinal herbs to treat AD. Actually, many drugs produced by the pharmaceutical industry are based on synthetic modifications of naturally occurring substances found in plants. As interest in herbal medicine has grown recently, so has scientific curiosity about how plants can be used medicinally to treat illness and enhance health, frequently without causing any noticeable side effects. The oldest treatments that mankind is aware of are herbal medications and natural products. Throughout history, the demand for herbal goods is now increasing tremendously all over the world **(**Olafsson, K., Jørgensen, et al., 1992; Pollock, B.G., Mulsant, et al., 1997**)**

Many medicinal herbs, including *Valerian officinalis*have been used nearly 10 years in many cultures to enhance memory **(**Burke, W.J., Dewan, V., et al., 1997)

Table 4: List of Potential Medicinal Plants Used in the Management of AD

Plant Name	**Family Name**	**Part of Plant**	**Reference**
Valerian officinalis	Honeysuckle	Root Part	Huang .B.,QinL.,et al.,1990
Punica-granatum l	Punicaceae	Flower Part	Katz, I.R., Jeste, et al., 1999
Saliva officinalis	Lamiaceae	Leaf Part	De Deyn, P.P., Rabheru, K., et al., 1999

Myrisctafragrans	Myristicaceae	Fruit Part	Street J., Clark WS., et al., 1999
Bacopamonnieri Linn	Plantaginaceae	Leaves And Stems	Neumann, P.J., Hermann, et al., 1999
Cenetellaasiatica Linn	Umbelliters	Whole Plant	Wimo, A., Karlsson, et al., 1997.
Evolvulusalsinoides Linn	Convolvulaceace	Leaf Extract	Akram, M. and Nawaz, A., 2017

3. Conclusion

A condition called dementia is characterized by a loss in function and intelligence. There have been many theories proposed for the pathophysiology of AD, but none have been able to fully explain the situation. Many times, the aetiologia of the disease is still unknown, therefore there are few treatments that may stop or reverse the disease's course however, some may temporarily lessen symptoms. Although, they have just been added to the list of potential treatments for AD, gene therapy and quantum dots have not yet received clinical approval.but also facilitates the inclusion of patients in the early stages of the disease for the purpose of conducting clinical studies of potential medication candidates. Promising diagnostic signs for AD include CSF fluid markers, volumetric MRI, amyloid imaging with concomitant indicators, and blood testing for inflammatory biomarkers. We have placed a strong emphasis on the use of immunotherapy, theranostics, and artificial intelligence .

Future Aspectives:- The BBB is one of the factors slowing down the development of AD treatments. Although various methods for breaking through the BBB and getting to the brain have demonstrated impressive efficacy, To establish the effectiveness of brain delivery, further study is required (e.g., dosage percentage/AD brain) in some animal models of AD. Additionally, patient-derived endothelial cell-based cellular neurovascular unit models may aid in improving knowledge of different BBB tactics. Leukocyte diapedesis and elevated integrin and adhesion molecules have recently attracted researchers' attention. However, because Further research is required because these studies are still in their early phases.

Conflict of interest:-The authors state that they have no financial or other conflicts of interest.

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