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An investigation into Alzheimer's disease, its current treatments, biomarkers, and risk factors

Yash Srivastav[1], Akhandnath Prajapati[2], Adityanath Prajapati[3], Madhaw Kumar[4], Mohammad Aqil Siddiqui[5]

[1,2,3,4,5] Goel Institute of Pharmacy & Sciences (GIPS), Lucknow, Uttar Pradesh, India

ABSTRACT

Alzheimer's disease (AD) is a neurological illness with a progressive course that is the most common cause of dementia in the global population over the age of 65 (50-70% of all dementia cases).This chronic and progressive disease causes deficiencies in a variety of brain functions (mostly at the cortical and hippocampal levels), including memory, reasoning, orientation, understanding, computation, learning ability, language, and judgement. Changes that contribute to cognitive impairment are accompanied by loss in emotional regulation and social behaviour. According to a research by Ferri et al.3, about 23.4 million individuals have dementia today, with 4.6 new cases identified each year, or one every 7 seconds. These rates are expected to increase every 20 years, with 81.1 million people suffering from dementia by 2040. Patients rarely have symptoms before the age of 50, but the disease's prevalence rises with age. His steady rise has caused medical, social, and economic concerns, particularly in countries with accelerated population ageing.As the world's elderly population ages, Alzheimer's disease (AD) and other kinds of dementia are becoming a growing public health concern among the elderly in developing countries. According to estimates, emerging countries will house nearly 70% of the world's population aged 60 and older by 2020, with India accounting for 14.2% of that figure. Dementia is predicted to affect 7.4% of people aged 60 and up in India. There are around 8.8 million Indians over 60 with dementia. Continue to investigate new treatments and therapeutic procedures in attempt to reduce the progression of the disease. Above all, given the neuropathological complexity of the illness, these measurements are designed for many targets and intended for use in the early stages of AD. If these future treatments are to be effective, doctors must develop new diagnostic procedures that will allow doctors to diagnose AD in its preclinical period (before symptoms occur) or perhaps forecast AD before it develops. AD prevention is a reasonable objective, but in order to attain it, we must first get a better understanding of the aetiology of the disease and how environmental and lifestyle variables influence the chance of developing the disease.

Keyword: Alzheimer's disease (AD), Epidemiology, Pathophysiology, Biomarkers, Nanotechnology, Risk factors.

INTRODUCTION

The most prevalent neurological condition in adults over 65 is Alzheimer's disease (AD). Author to whom letters should be addressed was formed by a small group of psychiatrists more than a century ago, in 1906.described the aberrant protein deposits that characterize the most prevalent neurodegenerative disorders in the brain.Alzheimer's disease (AD) is the neurological condition that most usually results in the loss of neurons and, ultimately, dementia. It was originally identified in 1906(1,2).A nosologic issue affects the study of Alzheimer disease (AD): Alzheimer disease has a number of various implications as a diagnostic term. In 1984, the phrase "probable AD" was coined to describe a clinically confirmed case of amnestic dementia that had progressed and was acquired, but for which no other etiological explanation could be found(3).There is a challenge in the study of Alzheimer disease (AD): The term "Alzheimer disease" has numerous distinct meanings in diagnostic terminology. The basic meanings of each interpretation, which each represent a model that denotes a different feature of the disease, differ strikingly from one another. (4,5).The most prevalent cause of dementia, Alzheimer's disease, is a significant public health issue. The neuropathologic observations of amyloid plaques and neurofibrillary tangles including tau serve as significant molecular hints to the pathophysiology. Although intricate, genetic factors are well acknowledged. Amyloid precursor protein, presenilin 1, and presenilin 2 gene mutations have been linked to three uncommon forms of autosomal-dominant early-onset familial Alzheimer

disease(6).Memory loss, slowed thinking and reasoning, as well as personality and behaviour changes are all symptoms of Alzheimer's disease (AD), an incurable and degenerative neurological ailment(7,8).Alzheimer's disease comes in two different forms: early-onset and late-onset. There is a hereditary component to both sorts.Elderly people's physical and mental health are gravely jeopardised by AD. The largest risk factor for the illness, whose incidence doubles every five years after the age of 65, is ageing(9).Worldwide, AD affects over 40 million people over the age of 60, and the number of patients is growing, doubling every 20 years(10–13).As the world's old population is rapidly ageing, Alzheimer's disease (AD) and other forms of dementia are becoming a rising public health concern among the elderly in emerging nations.According to estimates, emerging nations will house almost 70% of the world's population aged 60 and older by 2020, with 14.2% of them being India.In India, the prevalence of dementia among persons 60 and older is estimated to be 7.4%. Over 60-year-old Indians with dementia number about 8.8 million.(14).By 2025, the World Health Organization estimates that 1.2 billion of the world's elderly people will reside in low- and middle-income nations, or roughly 75 percent of them(15).Most Asian and Latin American countries have high (over 5%) age-adjusted estimates of dementia prevalence. However, sub-Saharan Africa and India appear to have lower prevalence rates of dementia (1-3%). According to epidemiological studies carried out in India between 1996 and 2006, AD is the most frequent cause of dementia (1.3%), which affects 2.7% of the population(16).

ALZHEIMER'S DISEASE CLASSIFICATION

AD is typically categorized based on when it first manifests. 1-5% of AD cases show an earlier onset, often in the late 40s or early 50s (so-called early-onset AD), with the majority of individuals (>95%) who develop this disease being older than 65 years (so-called late-onset AD).

- **Early-onset Alzheimer disease:**

Presenilin genes (PSEN1 and PSEN2), which encode proteins involved in the breakdown of APP and the production of A, and APP itself have all been strongly linked to the pathophysiology of early-onset AD. As 'diagnostic biomarkers' of the disease, AD-linked mutations in these three genes are characterized by strong penetrance (>85%), a predominance of autosomal dominant inheritance, and a certainty of A aggregation and early disease start. About 0.1% of instances of AD are caused by APP mutations. Since the mutations are located in or close to the A-coding exons (APP exons 16 and 17), the processing of the encoded protein is affected by the majority of dominantly inherited AD-linked missense mutations in β-amyloid precursor protein (APP) (17).

- **Late-onset Alzheimer disease:**

The late-onset AD genes are not inherited in a Mendelian manner and increase disease risk. First-degree relatives of patients with late-onset AD have a lifetime risk of the disease that is twice as high as that of unaffected first-degree relatives(18).Additionally, AD is more common among monozygotic than dizygotic cotwins, indicating that genetics play a significant role in this condition. In the largest twin research of dementia, which included 11,884 patients from the Swedish registry who were over 65 years old, 395 twin pairs were found to have AD in one or both of the twins(19).The single known susceptibility gene for late-onset AD, APOE, is located on chromosome 19 in a cluster with the genes for apolipoprotein C1, C2, and the translocase of outer mitochondrial membrane 40 (TOMM40). One of the three common isoforms of the lipid-binding protein APOE, which is encoded by three distinct alleles, namely APOE 2, APOE 3, and APOE 4, is expressed in humans.A single copy of the APOE 4 allele is linked to a 2- to 3-fold increase in the risk of AD, whereas two copies of the allele are linked to a 5-fold increase in the risk of the condition. The age of onset of AD is lowered by 6-7 years for each inherited APOE 4 allele.Additionally, the existence of this gene is linked to dementia development from MCI and memory impairment(20–23).

Late-Onset Alzheimer's	Early-Onset Alzheimer's
Signs begin to show in a person's mid-60s.	Between a person's 30s and mid-60s, signs begin to show.
Most common type.	Very rare.
Possibly involving the APOE ε4 gene.	Typically brought on by genetic abnormalities that parents pass on to their children.

Fig.1:Alzheimer's Disease: Some Differences Between Early- and Late-Onset.

The Symptoms And Signs

There are minor to very severe signs of dementia caused by Alzheimer's disease. Mild cognitive impairment, which manifests as memory loss, poor judgement, mood swings, frequent questioning, and trouble performing mathematical computations, is one of many symptoms of AD. Moderate AD symptoms include difficulties learning new things, trouble recognizing individuals, hallucinations, delusions, paranoia, and impulsive behavior's(24).Problems remembering recent events are frequently the first sign of moderate Alzheimer's disease. Other symptoms include losing things, getting lost in familiar surroundings, having trouble with complex tasks like paying bills, and experiencing mood and personality changes.

The signs of mild Alzheimer's disease include worsening memory loss and disorientation, worsening mood and personality changes, which can include aggression or paranoia, failing to recognize family and friends, and needing assistance with daily activities like dressing or using the restroom.The inability to talk and utter reliance on others for all daily activities are signs of severe Alzheimer's disease(25).

Alzheimer's Disease Epidemiology

Due in part to women's longer lifespans, the incidence and prevalence of AD are higher as people get older. Between the ages of 65 and 70 and over the age of 85, AD incidence is between 1% and about 4%. More than 1.3 million additional cases are anticipated in the United States annually by 2050, up from about 420,000 in 2000(26).The lowest recorded estimate of AD prevalence is 3% of the population at age 65, while the highest reported estimate is 47% of those over the age of 85. In the United States, 4.5 million people were thought to have AD in 2000. This number will nearly triple by 2050, reaching 13.2 million. With around 63,000 fatalities annually and a death rate of 21.8 per 100,000 people in the US, AD is currently the eighth greatest cause of death(27,28).A little more than 6% more people die from AD each year. Recent estimates place the median survival from the time of the initial diagnosis at 4.2 years for males and 5.7 years for women(29,30).

Pathophysiology Of Alzheimer's Disease:

The pathophysiology of AD has been a topic of discussion since the time of Alzheimer in 1907, when he first noticed the neuropathological signs of the disease, such as amyloidal plaques and hyperphosphorylated NFTs. In order to explain this complex illness, several hypotheses have been proposed based on the various causal components.for instance, the cholinergic hypothesis, the Ab hypothesis, the tau hypothesis, and the inflammatory hypothesis. The most widely accepted Ab hypotheses, in use for the past 20 years, have recently been demonstrated to not explain the intricate biology of this crippling disease(31,32).On a broad scale, the pathophysiology of Alzheimer's disease (AD) can be described as the progressive loss of brain tissue. Neurons die in a precise pattern over time as the condition worsens. Memory loss, especially in short-term memory recall, is one of the early symptoms of AD. The cortex, in particular the hippocampus, is one of the parts of the brain involved in remembering(33).In addition to subcortical nuclei like the serotonergic dorsal raphe, noradrenergic locus coeruleus, and the cholinergic basal nucleus, neuronal loss and/or pathology may be present in the hippocampus, amygdala, entorhinal cortex, and the cortical association areas of the frontal, temporal, and parietal cortices.

The trans-entorhinal cortex, the entorhinal cortex, the CA1 region of the hippocampus, and finally the cortical association areas, where the frontal, parietal, and temporal lobes are most affected, are the first sites where tangles are deposited. More so than the quantity of amyloid plaques, the degree and location of tangle development are strongly correlated with the severity of dementia(34).The accumulation of tau proteins is inversely correlated with hippocampal atrophy, cognitive decline, and brain atrophy. In the neuropathology of Alzheimer's disease, there is a loss of neurons and atrophy in the temporofrontal cortex, which results in inflammation and the deposition of amyloid plaques, an abnormal cluster of protein fragments, and tangled bundles of fibres. As a result, there is an increase in the presence of monocytes and macrophages in the cerebral cortex, and it also activates the microglial cells in the parenchyma(35).

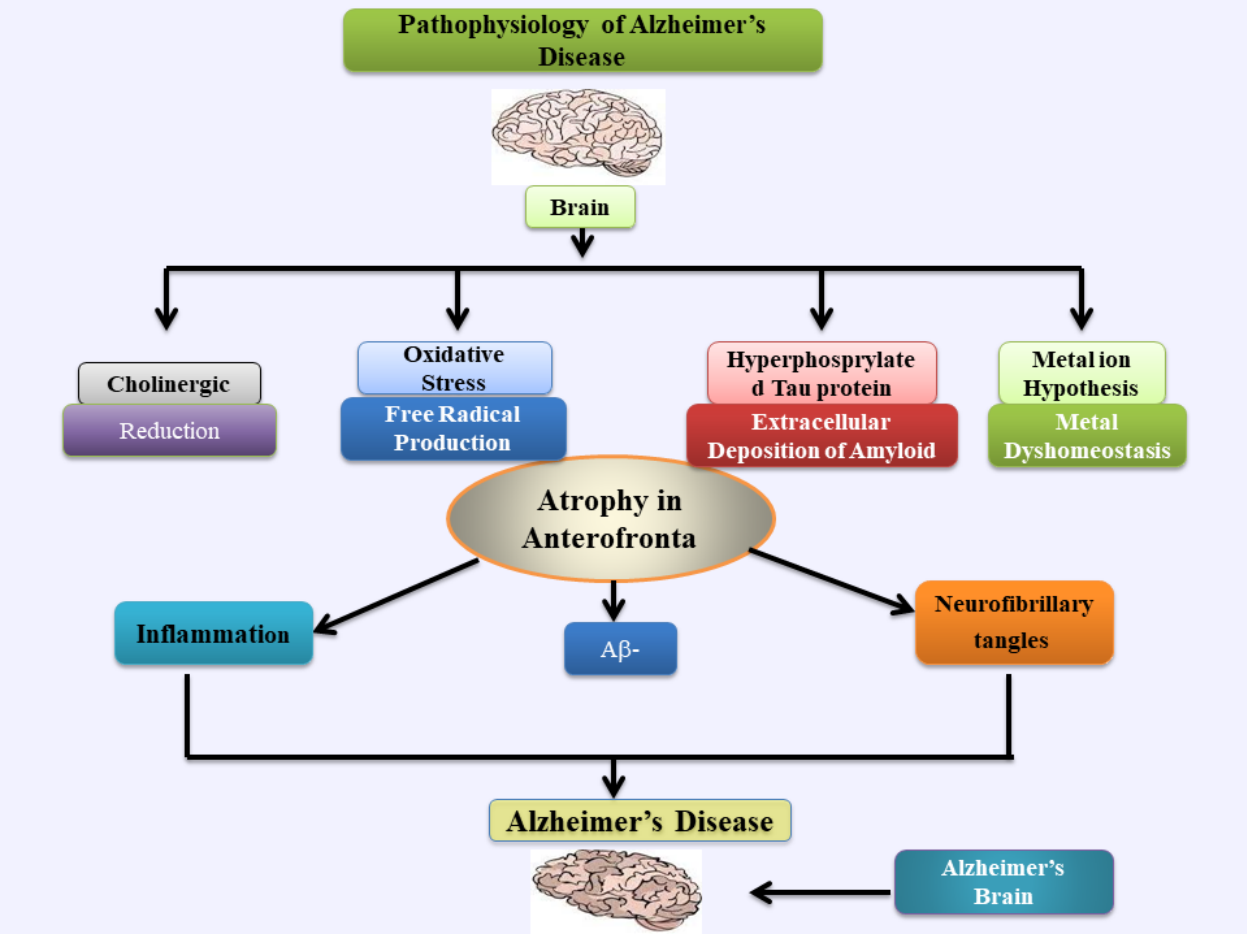

Fig.2:Alzheimer's Disease Pathophysiology(36).

BIOMARKER FOR ALZHEIMER'S DISEASE

A biomarker is a biological observation that stands in for and, ideally, predicts a clinically significant endpoint or intermediate outcome that is more challenging to see. Clinical biomarkers are typically assessed over shorter time periods than the final clinical outcome, making their application simpler and less expensive. They can be utilized for cell type identification, pharmacodynamic and dose-response investigations, prognostic markers, generating individualized therapeutic interventions, predicting and treating adverse drug reactions, and monitoring disease(37).In the process of developing drugs for Alzheimer's disease, biomarkers can be extremely helpful in identifying the best therapeutic candidates for costly phase 3 clinical trials. Along with a positive impact on the clinical course, biomarkers will be crucial for showing that a treatment modifies the underlying pathophysiology of the disease, which is necessary for classifying the medicine as having a disease-modifying effect(38).With varying degrees of success, new treatments are being explored for AD. There are reportedly roughly 28 drugs in phase 3, 74 in phase 2, and 30 in phase 1 clinical investigations, according to a recent analysis, but the failure rate due to a lack of effective treatment options is significant(39,40).It is believed that once the neuropathological threshold is crossed, no amount of treatment will be able to stop the progression of the illness(41). To ensure a strong impact from disease-modifying medications, there is an urgent need for biomarkers that can identify patients with MCI and early stages of AD. Currently, the biological or molecular hallmark of the disease, for instance, can be used to identify AD in individuals at the preclinical stage in vivo(42).For example, in patients with dominantly inherited Alzheimer's disease (AD), a change in the level of cerebrospinal fluid (CSF) amyloid beta (A) was found at 25 years and CSF-P-Tau at 10 years prior to the development of symptoms(43).Neurodegeneration starts just before clinical AD symptoms, such as the onset of cognitive impairment, as a result of cumulative Tau and A pathologies and cellular malfunction in the brain. Identifying neurodegenerative alterations precisely is difficult because they are seen in older people with cognitively normal functions.Additionally, the severity of the cognitive impairment is correlated with the growth of Tau diseases, which can themselves cause neurodegeneration.Although the effects of A and Tau abnormalities on brain physiology in AD are well known, their emergence and accumulation are due to early immune system dysfunction and developing

neuroinflammation(44–47).Epidemiological data associating AD to a history of infection or diabetes raises the possibility that infection may be a trigger for AD pathogenesis. In fact, A, which is generally removed by microglia, has the ability to activate them, causing the production of chemokines and local inflamation. Additionally, increased Tau phosphorylation and ensuing neurodegeneration are brought on by the spread of infection(48–50).The National Institute on Aging-Alzheimer's Association recently developed a study strategy regarding the diagnostic criteria. This approach uses an A/T/N classification scheme for AD biomarkers and is designed for observational and interventional research. It views AD in a biological rather than syndromal setting. The biomarkers of neurodegeneration are denoted by "N" in this approach, "T" denotes the amount of Tau biomarkers, and "A" denotes the concentration of A biomarkers. This system enables the classification of AD indicators in accordance with the pathological process and establishes their involvement in AD pathogenesis(51,52).Cell-free miRNAs can be employed for AD diagnosis or monitoring in addition to protein markers. A network of 250 miRNAs linked to AD was cross-validated in the literature as part of a recent systematic review, and the results showed a cluster of 10 miRNAs that might identify the condition 20 years before it manifested. The invasiveness of the test is one of the key considerations in the creation of AD biomarkers. Current diagnostic techniques relying on protein analysis in the CSF and positron emission tomography (PET) imaging are rather invasive and very expensive. The quest for suitable and least intrusive biomarkers of AD based on sources of blood, saliva, ocular fluids, and olfactory fluid is therefore a major effort(53,54).

- **Antibodies**

As it alters Aβ- and Aβ -1-levels, intravenous immunoglobulin or pure A-antibodies may be suggested as a therapeutic treatment for Alzheimer's disease(55).

- **Galanthamine**

Galanthamine separation has become a crucial therapeutic strategy for delaying the degradation of neurons in Alzheimer's disease in recent years, carried out by many Amaryllidaceae plants (Leucojum spp, Narcissus species, Galanthus spp)(56).Long-term therapy with galantamine is well tolerated.Galanthamine, sold under the brand name Nivalin, is already marketed in Germany and Austria for other indications such facial neuralgia and has already received approval in Austria for AD(57).

- **Multi-target-directed ligand (MTDL)**

In the multifaceted etiology of the disease, multi-target-directed ligand (MTDL) moves towards with the potential approach to find novel AD medications. The majority of new compounds have heterodimeric structures that enable them to interact with a variety of targets when combined with pharmacophores; they may be derived from nature or be previously used medications (tacrine, donepezil, galantamine, memantine). Some of the drugs discussed here seem to be potential medication treatments, while others could serve as valuable inspiration for researchers looking for novel and potent treatments for AD(58).

- **Cannabinoids**

AD treatment options now include using the cannabinoid system. The cannabinoid consists of several cannabinoid receptors (CB), including the well-known CB1 and CB2 receptors. Results show that activating both CB1 and CB2 receptors with natural or synthetic agonists at non-psychoactive doses has positive effects in Alzheimer experimental models by lowering harmful beta amyloid peptide action and tau phosphorylation as well as by encouraging the brain's natural repair processes(59).

- **Poly-phenolic compounds**

Due to their potent antioxidant, anti-inflammatory, anti-microbial, and anti-tumor properties, polyphenolic chemicals have come to be recognized as natural sources for treating a wide range of ailments, including neurological problems. A growing body of research indicates that polyphenolic chemicals, which come from a number of sources, can enhance brain damage and cognitive function in animal models of AD(60).

- **Metals and Stem cells**

In some neurodegenerative illnesses, such as Alzheimer's disease, lithium has also been considered a neuroprotective agent and a potential therapeutic candidate. Lithium regulates a number of homeostatic systems involved in neurotrophic response, autophagy, oxidative stress, inflammation, and mitochondrial function, which underlies its purported neuroprotective benefits. Such a broad spectrum of intracellular reactions may be a result of lithium's two main effects, which include its suppression of the enzymes inositol monophosphatase (IMP) and glycogen synthase kinase-3 beta (GSK-3). Stem cells may be used in the treatment of AD, according to recent preclinical research. The methods of stem cell-based therapy for AD include neuroprotection and trophic action, anti-amyloidogenesis,

favourable regulation, and neuron replacement. The pathophysiology of familial and sporadic AD can be studied, and anti-AD medications can be screened. AD can be modelled using iPSC(61).

- **Metal complexes**

Long-lived fluorescent ruthenium and iridium metal complexes that significantly alter their electronic spectra when bound to A fibrils may serve as effective probes to learn more about the molecular processes behind amyloid production and aggregation. A peptide of different lengths interacts with complexes with the kinetically inert ions to produce adducts with different toxicity and aggregation propensities. Metal complexes must meet the demanding standards of therapeutic medicines in order to have a chance of being effective therapeutic inhibitors of amyloid production and A toxicity(62).

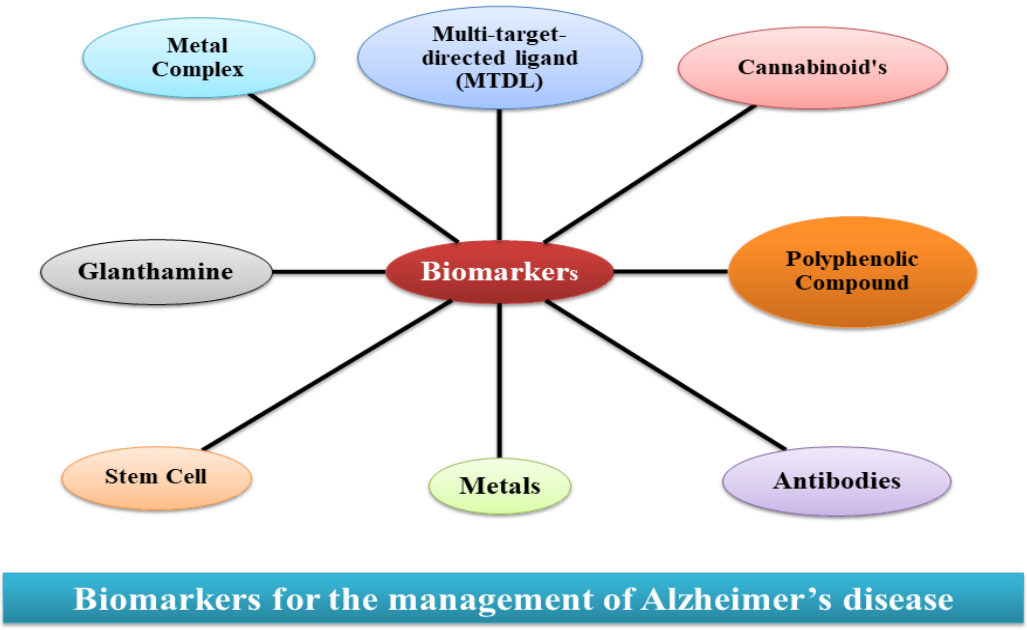

Fig.3:Alzheimer's disease management using biomarkers(36).

MEDICATIONS THAT CAN TREAT ALZHEIMER'S

The majority of the tissue specimens that are now available come from advanced stages of the disease, making it challenging to investigate disease beginning processes and the course of AD in humans. As a result, in vitro research and the use of animal models for AD are the main methods used by researchers studying Alzheimer's disease. P1 adenosine receptors and P2 nucleotide receptors for ATP, UTP, and their metabolites make up the extensive family of proteins known as purinergic receptors. Several physiological and pathological processes, including neuroinflammation, have been found to be regulated by this family of receptors. They may also play a role in the etiology of neurodegenerative illnesses like AD(63).There have been reports of many illness indicators, including amyloid deposits surrounding neurons, hyperphosphorylated tau protein, oxidative stress, bio-metal dyshomeostasis, low levels of acetylcholine, etc.

The majority of receptors in the central nervous system are G-protein coupled receptors, which are also connected to intricate downstream pathways that can be altered for therapeutic purposes. The A peptide is the primary cause of the pathogenic cascade that results in dementia and other symptoms of AD, according to the amyloid hypothesis(64–66).Studies have demonstrated that oxidative stress-induced respiratory chain malfunction, loss of mitochondrial biogenesis, abnormalities of mitochondrial dynamics, and mtDNA mutations are all signs of mitochondrial dysfunction, which has been linked to AD. The mitochondria may be a drug therapy target for AD. The available AD medications do not specifically target mitochondria.

The only two types of medications recognized by the FDA for treating AD are cholinesterase inhibitors (galantamine, donepezil, and rivastigmine) and N-methyl-d-aspartate receptor antagonist memantine(67).Pharmacologic approaches

have been centred on controlling neurotransmitter changes brought on by disease; these approaches can be classified as symptomatic or neuroprotective. Although a neuroprotective therapy will have a cumulative benefit that lasts even after the medication is stopped, symptomatic and neuroprotective pharmacologic treatments may have identical clinical trial result features. The effectiveness of current treatments, such as cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists, is evaluated by how well they can prevent the onset of symptoms in the cognitive, behavioural, and functional domains. Based on the "cholinergic hypothesis" of memory failure, early pharmacologic treatments for AD aimed to improve cholinergic transmission in the brain. Acetylcholinesterase (AChE) inhibition has so far been the most effective method for raising synaptic levels of acetylcholine (ACh) because it prevents ACh from being broken down. It may help improve cholinergic transmission to inhibit the butyrylcholinesterase (BuChE) enzyme, which is a small component in healthy brains but is amplified in AD patients' brains in connection with plaques and tangles(68).The FDA has authorized a total of five medications designed to reduce the symptoms of Alzheimer's disease. A brand-new medication called Namzaric (donepezil and memantine) was authorized in 2014.

The five medications work through two distinct processes. One is cholinesterase inhibition, which slows the progression of Alzheimer's disease by preventing acetylcholine's essential neurotransmitter breakdown. This class of medications includes galantamine (Razadyne), donepezil (Aricept), and rivastigmine. The second drug is memantine (Namenda), a non-competitive NMDA channel blocker that lowers the activity of the neurotransmitter glutamate, which is crucial for memory and learning because it binds to the NMDA receptor(69).The primary pathogenic features of AD are left untouched by current pharmaceutical treatments, which only treat the symptoms.

It is crucial to create innovative, efficient treatments for this reason. For Alzheimer's disease, there are numerous potential treatments. Researchers are looking into novel therapeutic strategies, such as those that are more directly aimed at the disease's pathogenesis. The amyloid-peptide vaccine, secretase inhibitors, pharmaceuticals that decrease cholesterol, metal chelators, and anti-inflammatory medications are some of these potentially disease-modifying therapies(70).

Many natural products and dietary components, including antioxidants and anti-inflammatory compounds, have been studied for their therapeutic potential in the treatment of AD. A small pharmacological pipeline is available, and many therapeutic targets have been researched for treating AD. Despite these efforts, developing drugs for AD has proven to be very challenging, and the majority of clinical trials have produced unimpressive outcomes(71).Several potential treatments are now being researched, including monoamine oxidase-B (MAO-B) inhibitors, oestrogen replacement therapy, anti-inflammatory drugs, and free radical scavengers and antioxidants. It is debatable and mostly dependent on retrospective research that oestrogen or non-steroidal anti-inflammatory medications (NSAIDs) have a protective effect.

To conclusively prove the advantages of long-term oestrogen or NSAID use in AD prevention, more controlled prospective studies are required. Although selective prevention MAO-B inhibitors like Lazabemide and free radical scavengers or antioxidants like idebenone are well tolerated, further research is necessary to prove their preventive efficacy.Additionally, their strategies—which include anti-amyloid medications that influence beta amylase secretion, aggravation, and toxicity—seem promising. Meanwhile, medications that prevent the formation of neurofibrillary tangles and induce nerve growth factor (NGF) are still in the very early stages of development(72).Non-genetic alterations that affect learning and memory, including as DNA methylation and histone modifications, have lately been identified as promising prospective targets for AD treatments. The pathogenic pathways for AD include dynamic and latent epigenetic changes, which offer useful reversible targets for AD and other neurological illnesses(73).

It has been proposed that one pathogenic element behind this neurodegenerative condition is a change in the metabolism of insulin in the brain. According to this hypothesis, Alzheimer's patients exhibit lowered brain insulin receptor sensitivity. An excellent justification for the hypothesis that pharmacological methods for enhancing brain insulin signalling, such as the administration of insulin(intra nasaly), could have important potential in the treatment and prevention of AD is that insulin reduces the hippocampal synapse vulnerability to beta amyloid, a peptide thought to be responsible for the development of Alzheimer's disease(74).

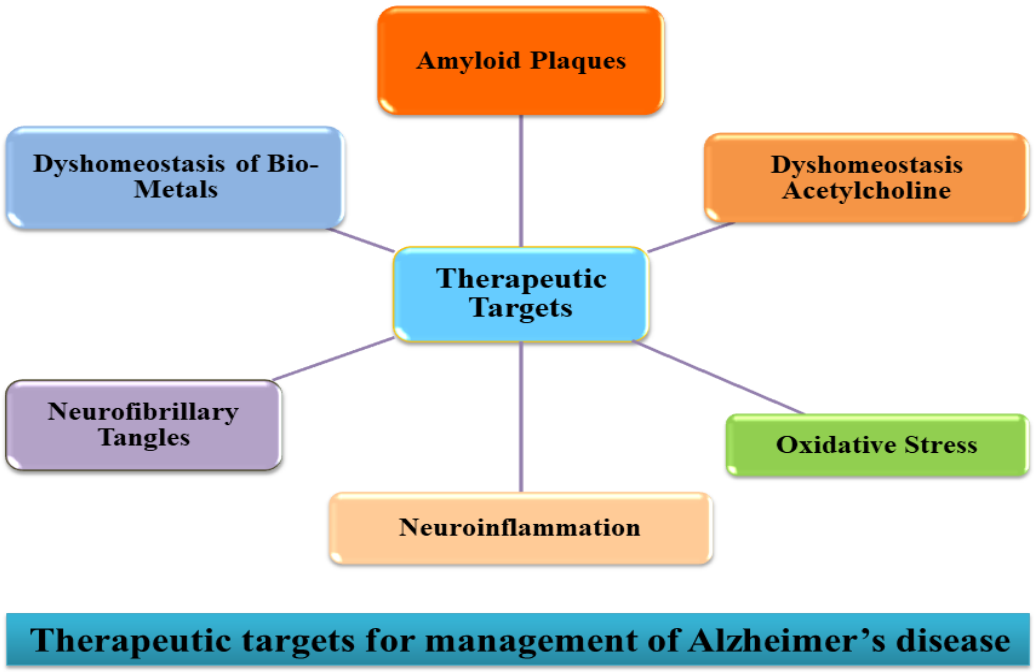

Fig.4:Management of Alzheimer's disease through therapeutic targets(36).

ALZHEIMER'S DISEASE TREATMENT WITH NANOTECHNOLOGY

AD diagnosis is improving thanks to nanotechnology. The creation of disease-related biomarkers in cerebrospinal fluid has drawn a lot of interest recently. Among the diagnostic targets (ADDL) were the tau protein, the amyloid precursor protein (APP), the 42-amino-acid form of -amyloid (A42), and amyloidderived diffusible ligands. Dementia and ADDL levels in the cerebrospinal fluid have been connected. It is simpler to assay these proteins thanks to the use of ADDL-specific monoclonal antibodies in bio-barcode amplification, an ultrasensitive nanoparticle-based protein detection method. The bio-barcode amplification increases detection sensitivity by using nanoparticles as DNA carriers(75).The addition of gold nanoparticles is another new development. An antibody's Aβ subunit was joined to gold nanoparticles that bind to the Aβ protein. Scan tunnelling microscopy was used to detect the immunocomplexes that were produced at quantities as low as 1 fg/mL. Gold nanoparticles are also used to create multispot-localized surface plasmon resonance immunochips, which can track tau at 10 pg/mL(76).

- **Liposomes**

As sphere-shaped vesicles, liposomes are constructed from one or more phospholipid bilayers. In numerous scientific disciplines, including as mathematics, theoretical physics, biophysics, chemistry, colloid science, biochemistry, and biology, they are now important resources, reagents, and instruments. Since then, liposomes have entered the market. Numerous formulations of liposomes are currently being used in clinical settings. Liposomes are innovative new drug delivery techniques that exhibit cutting-edge technology to transfer active chemicals to the site of action. In addition to being non-immunogenic, flexible, less poisonous, biodegradable, and biocompatible, liposomes were initially discovered in the 1960s(77,78).A curcumin derivative and a BBB transport mediator anti-transferrin antibody (TrF) were included in the polyfunctional liposomes made by Mourtas et al. in 2004. According to the post-mortem brain samples of AD patients, liposomes containing the curcumin derivative or the curcumin derivative combined with anti-TrF showed a strong affinity for amyloid plaques. According to the authors, curcumin-derived liposomes do not prevent or decrease aggregation or deposit staining(79).

- **Cubosomes**

Cubosomes are extremely stable nanoparticles produced by the lipid cubic phase and stabilized by an outer corona comprised of polymers. A single lipid bilayer creates a continuous periodic membrane lattice structure with holes produced by two interlaced water channels in lipid cubic phases. These liquid crystalline nanostructured carriers are biocompatible. A 3-D organisedbicontinuous curved lipid bilayer is separated from the bioactive chemicals and proteins

by two water channels.They are good carriers for a range of drug administration routes because they can encapsulate amphiphilic, hydrophilic, and hydrophobic molecules, maintain controlled drug release and bio-adhesion, and be thermodynamically stable(80).To target AD in the brain, Elnaggar et al. created piperine-loaded Tween-integrated monoolein cubosomes (T-cubs) in 2015(81).

- **Lipoprotein-Based Nanoparticles**

The liver and intestines produce heterogeneous nanoparticles called lipoproteins (LPs), which circulate in the bloodstream. Through cell membrane receptors or LP lipase on the cell surface, LPs are crucial in the transport of dietary and endogenous lipids to target cells. Since they are known to have a strong affinity for A, lipoprotein-based nanoparticles can be broken down more quickly and are used for both therapeutic and diagnostic purposes. In order to remove A, Song and coworkers developed a nanoparticle system in 2014 that contained apolipoprotein E3-reconstituted high-density lipoprotein (ApoE3-rHDL). One hour after IV administration, approximately 0.4 percent IDg1 (injected dose per gramme) of ApoE3-rHDL reached the mouse brain. After a month of daily treatment, neurological abnormalities, microgliosis, A deposits, and other conditions.But it hasn't yet been determined how hazardous it is. Tarenflurbil (TFB) distribution to the brain via the intranasal route (TFB-SLNs) was studied in 2012 by Muntimadugu et al. using solid lipid NPs or TFBloaded poly(lactideco-glycolide) NPs (TFB-NPS)(82,83).

- **Antibody-Tethered Nanoparticle**

The neutralisation of antigens and the activation of the complement system are both carried out by antibodies. Antibody conjugation to nanoparticles, which are biological items that are nanosized, was created to reduce immunological reactions and is now often used in research and diagnosis. Tamba and colleagues looked at the mouse BBB's ability to block the passage of glucose (Glu) and glucose-poly(ethylene glycol) methyl ether amine (Glu-PEG)-coated fluorescent silica NP derivatives (Ru@SNPs) in 2018. Surprisingly, it was shown that silica NP compounds could readily cross the BBB and function as effective drug-delivery moderators, entering the brain by both particular and general pathways(84,85).

- **Polymeric Nanoparticles**

The ascorbic acid-added PEGylated PLGA polymeric matrix that makes up the polymeric nanoparticle (PNP) system in this study was created in an antioxidant environment. Ascorbic acid and nanoencapsulation both protect the chemical structure of EGCG and prevent it from being cleared in vivo, thereby boosting its bioavailability and activity. This work's PNP system is composed of a PEGylated PLGA polymeric matrix that was created in an antioxidant environment with ascorbic acid addition. In order to increase EGCG's bioavailability and activity, ascorbic acid and nanoencapsulation both secure the substance's chemical makeup and shield it from in vivo clearance. Without having any negative effects on various organs, this PNP increases neuronal cell viability, improves cognitive and memory impairments in treated mice, and prevents organ damage(75).A curcumin/selenium combination carrier was created by Huo et al. with the goal of reducing A aggregation. This nanocarrier specifically binds A oligomers, creating new routes for the targeted drug. Vilella and colleagues developed a zinc-loaded polymeric nanocarrier with the coating of peptide, which is responsible for BBB penetration, enabling more precise targeting(86,87).

- **Curcumin-Loaded Nanoparticles**

In recent decades, curcumin has been studied and it has been proposed that it has a wide variety of biological activities due to its wide range of bioactivity, which includes anti-AD properties and possibly neuroprotective effects. Despite these benefits, curcumin has a low bioavailability, does not enter the biological system, and is vulnerable to oxidation and biodegradation. Therefore, by encapsulating it inside nanocapsules, this barrier can be reduced to improve BBB crossing(88).As demonstrated in silico and by modelling, Brambilla et al. produced a batch of high molecular weight glycolated polyethylene nanocarriers linked to A1-42 in 2012. These nanocarriers were capable of changing conformation in serum(89).Additionally, it has been proposed that they be used as an MRI contrast agent to identify A plaque(90).

- **Nanoparticle–Biomolecule Conjugates**

The surface of a nanoparticle-biomolecule conjugate contains biomolecules. Nanoparticles are microscopic objects used in nanobiotechnology to study the functions of biomolecules. In 2014, Zhang et al. developed a spherical, dual-function drug delivery system that includes the peptide TQNP/H102, a -sheet breaker. To enable A42 targeting and BBB passage, respectively, QSH- and TGNtargeting peptides were linked to the nanoparticle surfaces. A highly specialized type of AD treatment is now possible because to this kind of technology(91).

- **Magnetic Nanoparticles**

Nanoparticles that can be influenced by magnetic fields are known as magnetic nanoparticles. These particles typically consist of two parts: a chemically useful component and a magnetic component, which is commonly iron, nickel, or cobalt. Microbeads have a diameter of 0.5–500 m, whereas nanoparticles have a diameter of less than one micrometre (often 1-100 nm). Magnetic nanoparticle clusters made up of numerous individual magnetic nanoparticles have a diameter of 50–200 nanometers and are known as magnetic nanobeads. A magnetic-containing drug-guiding electromagnetic actuator was created in 2016 by Do et al(92).Magnetic particles were seen to flow through the BBB when exposed to electromagnetic fields of 28 mT (0.43 T/m) or 79.8 mT (1.39 T/m) externally. It was also shown that a pulsed magnetic field significantly increased the absorption and transportation speed of magnetic nanoparticles (MNPs) in the brain. MNPs are fascinating candidates for a range of biomedical tasks. They consist of a biocompatible coating, such as polyethylene glycol (PEG), and a magnetic core manufactured of maghemite. When MNPs are functionalized, such as when they are mixed with biological vectors, luminous labels, antibodies, medications, and other substances, they become more intriguing and helpful. These excellent MNPs are stable for extended periods of storage and unharmful to cells or tissues.Alzheimer's disease A plaques have been identified using targeted MNPs. For instance, Poduslo et al. targeted A plaques in Alzheimer's disease using a molecular probe that was loaded with gadolinium. After being administered intravenously, their clever technique was able to pass through the BBB and exactly connect to the plaques that were seen on MRI. They discovered that the cortical and hippocampus regions of AD-transgenic mice had improved by more than 9 times(93).Such tools not only hold great potential for early detection, but they can also be used to observe directly how well an anti-amyloid therapy is working. Therefore, these functionalized MNPs are being investigated as potential drug delivery systems in addition to A detection and noninvasive long-term therapeutic response assessments(94).

- **Nanoemulsions—Binary Drug Vehicular Systems**

To enhance the delivery of medicinally active ingredients, nanoemulsions are emulsions that are only a few nanometers in size. An emulsifying agent, such as a surfactant and a co-surfactant, is used to mix two immiscible liquids into a single phase in this thermodynamically stable isotropic system. Aspirin, methyl salicylate, nimesulide, gamma-tocopherol, caffeine, plasmid DNA, aspirin, and others use nanoemulsions for transdermal drug delivery. Curcumin-loaded nanoemulsion was made by Sood et al. and stabilised by a surfactant-cosurfactant mixture. The formulation was found to significantly enhance the water solubility of curcumin(95).A non-competitive NMDA receptor antagonist, memantine was first prescribed to treat influenza. The glutamatergic system is impacted, and blocking NMDA receptors stops glutamate from overstimulating these receptors.Additionally, the generated nanoemulsions display antioxidant activity, which may be beneficial for the treatment of AD, which is characterized by an increase in free radical generation. NEs are non-toxic and biocompatible with a 93.83% cell viability. The formulation was radiolabeled and administered to rats orally, intravenously, and transnasally to evaluate the drug's pattern of distribution. Gamma images of rats clearly display drug build-up in the brain following intranasal treatment.The radiolabeled formulation was more effectively absorbed in the brain when administered intranasally as opposed to intravenously. Memantine may be administered by intranasal spray to increase its effectiveness against AD, according to a report(96).Ketoprofen in a pullulan-stabilized nanoemulsion was the subject of research by Ferreira et al. A fast (5 h) release pattern with considerably greater bioavailability was discovered through in vitro experiments, and this increased brain permeability(97).

- **Inorganic Nanoparticles**

The possibility of inorganic nanoparticles (quantum dots) like silicon, carbon, indium, cadmium, silver, and graphene crossing the BBB has also been studied. Due of silicon's reputation as being biocompatible, silicon quantum dots are being investigated for therapeutic and diagnostic uses(98).The semiconducting nanoparticle known as graphene quantum dots (GQDs) is a powerful inhibitor of A peptide aggregation. GQDs can easily pass through the blood-brain barrier due to their small size. Additionally, GQDs have fluorescent characteristics that can be used to track A concentrations in vivo.In comparison to other carbon materials, GQDs have an advantage in the application and clinical investigations for AD due to their low cytotoxicity and strong biocompatibility. While larger quantum dots have a longer wavelength and a narrower band gap, smaller quantum dots have a wider band gap. QDs' chemical and physical properties are solely governed by their size.By changing the QD's size and chemical makeup, the fluorescence emission may be tuned from the near-ultraviolet to the visible and near-infrared spectrums, spanning a wavelength range of 400-2000 nm(99).

- **Optical Imaging**

The process of optical imaging uses light and the distinct properties of photons to produce in-depth images of organs, tissues, cells, and even molecules. The techniques offer minimally invasive or non-invasive ways to view within the body. Electroencephalography (EEG) should be utilized in conjunction with optical imaging to study neurological

changes brought on by blood flow interruption. In order to identify AD, optical imaging, a relatively recent technology, has been used in molecular biomarker imaging. Studies on optical imaging for medicinal use have also been conducted(88).

- **Aptamers**

The ability of nucleic acids is used by aptamers, which are RNA or single-stranded DNA oligonucleotides of 20–60 nucleotides. They function similarly to antibodies. With strong affinity, specificity, and a long shelf life, they exhibit minimal toxicity or immunogenicity. Due to their physicochemical properties, nanomaterials with minuscule particle size, enormous surface area, good absorption, and low immunogenicity are potential prospects for nanomedicine. In medical imaging and tagging, particularly in techniques like positron emission tomography (PET) and magnetic resonance imaging (MRI), aptamers with easy chemical alteration at both the 30 and 50 ends, along with excellent selectivity and target affinity, offer significant structural benefits(100).

- **Dendrimers—Macromolecular Drug Carriers**

Branching macromolecular formations called dendrimers are nanoscale in size. They have three structural components: the outer functionalized surface, the internal dendritic portion, and the central core(99).According to studies, dendrimers are employed as drug delivery systems for AD and can aid in the solubilization of medications that are only weakly soluble in aqueous solutions. In order to improve biocompatibility and synaptic breakdown against Ab oligomers and prevent memory loss in AD, poly(amidoamine) (PAMAM) dimers act as modulators of amyloid fibrillar formation. A new kind of dendrimer (G4HisMal) with a poly(propylene imine) core and a maltose-histidine shell was recently developed by Aso et al. to protect transgenic mice from AD-induced memory loss, boost BBB permeability, and improve biocompatibility. G4HisMal significantly enhanced biocompatibility and BBB penetration in their transgenic mice model of AD, maintained synapses, and prevented mental decline(101).

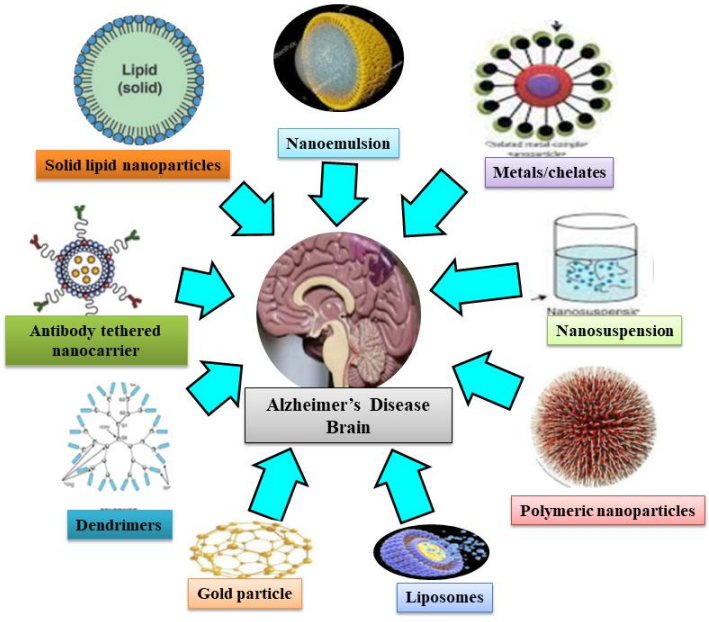

Fig.5: Alzheimer's disease is being treated with nanocarriers(102).

ALZHEIMER'S DISEASE-TREATING HERBAL MEDICATION

There are several popular traditional Indian plants that can be utilized to treat neurological illnesses like Alzheimer's and dementia. Ayurvedic Rasayana medications are abundant in anti-oxidants and immunomodulatory substances. It has already been established that some of these medications have high antioxidant properties. Many plants, including Ashwagandha, Brahmi, Mandukaparni, Shankapushpi, Vacha, Jatamansi, and Jyotshmati, fall under the category of Rasayana plants. These herbs are categorized as brain tonics or rejuvenators since they are particular to brain tissues(103).In addition to the aforementioned, various Rasayana medicines have been confirmed in our laboratory to have a positive effect on memory deficiencies, warranting their prospective function in dementia and other neurological disorders, as well as their potential benefit in AD(104–106).

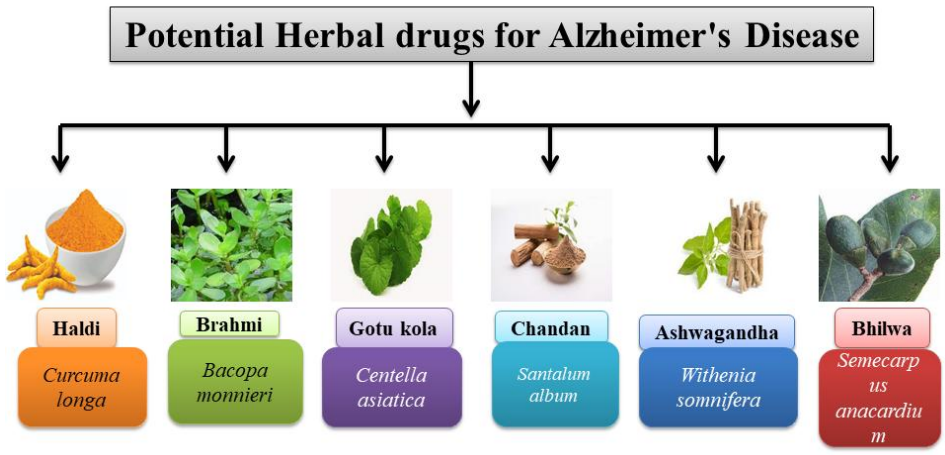

Fig.6: Herbal medicine for the treatment of Alzheimer's disease

- **Haldi**

An herbal medication with potential for treating AD is curcumin. When delivered to a mouse model of AD, curcumin (the main chemical component of haldi or turmeric) reduces the load of A in the brain and serum A levels. This impact is mostly apparent in the neocortex and hippocampus of the AD animal model(107).The blood-brain barrier is crossed by curcumin, which also prevents the development of Aβ plaques, the dissolution of A fibrils that have already formed, and the extension of those fibrils. Curcumin therapy has a higher therapeutic impact on AD and can restore the malformed neuritic morphology that is observed close to plaques. It is more effective than naproxen or ibuprofen at preventing the development of Aβ plaques. Amyloid precursor protein (APP) synthesis and expansion is a different mechanism that disrupts AD(108–111).It is possible that curcumin plays a function in modulating γ-secretase by reducing the synthesis of Aβ and presenilin1 gene expression. Additionally, curcumin's impact on APP maturation may potentially contribute to the decreased APP synthesis(112,113).The fact that curcumin and certain of its metabolites have demonstrated treatment potential for AD is interesting. Tetrahydrocurcumin, Hexahydrocurcumin, and Octahydrocurcumin are the most widely used metabolites of curcumin; they are reductive in nature(114,115).

- **Brahmi**

Since ancient times, brahmi (Bacopa monniera; family: Scrophulariaceae) has been prized as a brain tonic for reviving intellect, an anti-stress remedy for anxiety, and a way to improve cognitive abilities. According to numerous research, this medicinal herb can be used to treat neurological and mental diseases since it operates as a nervine and a mental tonic(116).

- **Chandan**

A member of the Santalaceae family, Chandan. As stated in siddha, this herb may have the ability to improve memory and cognitive function. Scopolamine-induced dementia patients' learning and memory are greatly improved by licorice due to its significant impact on memory-enhancing activities(116).

- **Gotu kola**

Centella asiatica, often known as gotu kola or mandookaparni, is a member of the Umbelliferae (family Apiaceae). It has been used to sharpen focus, improve memory, and promote alertness. It is a psychotropic medicinal herb that is employed in the treatment of stress and anxiety. It has been used to bolster the nervous system, revive youth, and improve memory. It's been applied to enhance memory(116).

- **Ashwagandha**

Withaniasomnifera, often known as ashwagandha, is a shrub that belongs to the solanaceae family. It is regarded as an adaptogen, a non-toxic drug that normalises physiological processes in response to prolonged stress by activating the immune and endocrine systems. By extending its neurite outgrowth, ashwagandha may aid in the repair of broken neural circuits(116).

- **Bhilawa**

An Anacardiaceae plant known as bhilawa (Semencarpus anacardium). It has anti-oxidant properties and functions as a brain tonic(116).

ALZHEIMER'S DISEASE NON-PHARMACOLOGICAL TREATMENTS

The use of no pharmacological therapies as adjuvants in other types of treatment or for the prevention of AD is crucial. The approaches to preventing AD can be split into two categories: lifestyle approaches and Diet.

- **Lifestyle**

Physical exercise, mental stimulation, energy restriction, and social interaction are among lifestyle choices that can help prevent AD(117).In a cohort study, physical activity like aerobic exercise was linked to a decrease in AD impairments. This wasn't in line with research that only looked at a handful of cases(118,119).In ageing animals, exercise was found to improve hippocampus neurogenesis and learning(120–122).The three mechanisms proposed to explain the neuroprotective effects of exercise include (1) the release of neurotrophic factors from synaptically active neurons, such as BDNF and insulin-like growth factor (IGF-1), nerve growth factor (NGF), and vascular endothelial growth factor (VEGF); (2) the reduction of free radicals in the hippocampal formation; and (3) the activation of CREB transcription factor(123–128).Mental difficulties may offer protection against cognitive deterioration and likely against AD, according to certain theories.Psychoeducation and computer classes have mediocrely positive impacts(129,130).The link between calorie restriction and brain motivation is crucial because, in the past, humans frequently needed to engage in rigorous exercise in order to obtain their food by killing wild animals(131).Phosphorylated tau and amyloid-β levels were shown to be lower in the brains of several AD animal models that were fed and underwent calorie restriction. Because SIRT1 was shown to be increased in p25 CK mice with traits like AD, it is possible that this protein, which has nicotinamide adenine dinucleotide-dependent deacetylase or adenosine diphosphate-ribosyltransferase activity, is connected to the potential mechanism. Additionally, resveratrol produces neuronal death prevention by stimulating SIRT I. In a rodent model of AD, SIRT produces an increase in α-secretase and a decrease in amyloid-β deposition in primary cultures. SIRT1 levels similarly rise with NADp in vitro(132,133).In a mouse model of AD, ghrelin was used to investigate the connection between hunger and neuroprotection. The results showed enhanced cognition in the water maze test as well as lower levels of amyloid- and inflammation(134).Lack of socialisation hinders the mental and physical development of people, and loneliness has been linked to a number of illnesses, including depression, alcoholism, obesity, diabetes, hypertension, Alzheimer's disease, and cancer(135).

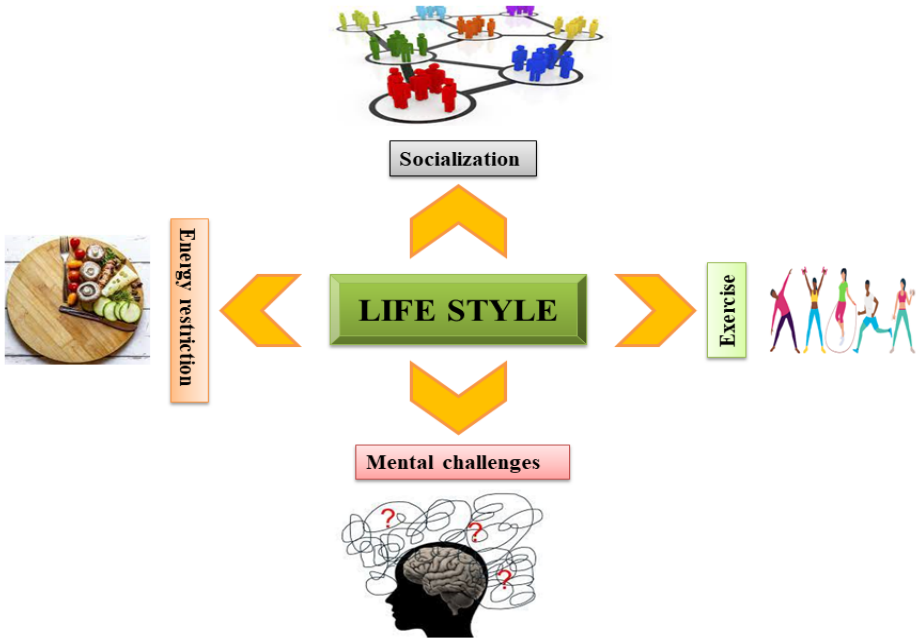

Fig.7:Alzheimer's disease therapy based on a person's lifestyle(136).

- **Diet and Chemical Substances**

Vitamins such as B6, B12, folates, and E, C, and D vitamins were evaluated as dietary supplements for Alzheimer's disease prevention. On the one hand, a two-year treatment with homocysteine and vitamin B in 271 individuals showed a significant difference in whole brain atrophy compared to placebo, however other investigations show different findings(137–140).Folic acid may have neuroprotective action via an epigenetic mechanism that suppresses amyloid-β peptide formation. Studies with 2000 IU of vitamin E did not show a protective benefit against Alzheimer's disease after

three years of treatment, not when paired with vitamin C. Furthermore, vitamin D administration boosts cognitive performance(141–143).In terms of chemical substance intake, alcohol studies show a relationship between the prevention of AD and modest levels of red wine consumption due to its polyphenol content, but drinking alcohol frequently was related with an increased risk of dementia. Glucosamine, omegas 3 and 6, which generate interleukins or prostaglandins for inflammatory reactions, and antioxidants such as beta-carotene and lycopene 6 have all been postulated as neuroprotective compounds(136,144–146).Other investigations of chemical substances associated to probable protection against neuropsychiatric illnesses such as Alzheimer's were those involving the consumption of plants and their secondary metabolites: flavonoids, alkaloids, or terpenoids. Flavonoids are regarded safe, and neuroprotection has been demonstrated in 90 patients treated with flavanol. Flavonoids also inhibit acetylcholinesterase and improve memory, in addition to decreasing glutamate release(147–152).

ALZHEIMER'S DISEASE RISK FACTORS

Alzheimer's disease is thought to be a complex disease with multiple risk factors, including growing age, hereditary factors, head injuries, vascular diseases, infections, and environmental variables (heavy metals, trace metals, and others). The underlying aetiology of Alzheimer's disease pathological alterations (A, NFTs, and synaptic loss) is yet unknown. Several hypotheses have been proposed as causes of AD, but two are thought to be the most important: some believe that cholinergic dysfunction is a critical risk factor for AD, while others believe that an alteration in amyloid - protein production and processing is the main initiating factor. However, there is currently no recognized explanation for describing the pathophysiology of Alzheimer's disease(153,154).

- **Environmental Factors**

All cases of Alzheimer's disease cannot be explained by ageing or genetic risk factors. Environmental risk factors such as air pollution, nutrition, metals, infections, and others can cause oxidative stress and inflammation, raising the likelihood of developing Alzheimer's disease. In this section, we discuss the most important environmental factors and their associations with Alzheimer's disease(155,156).

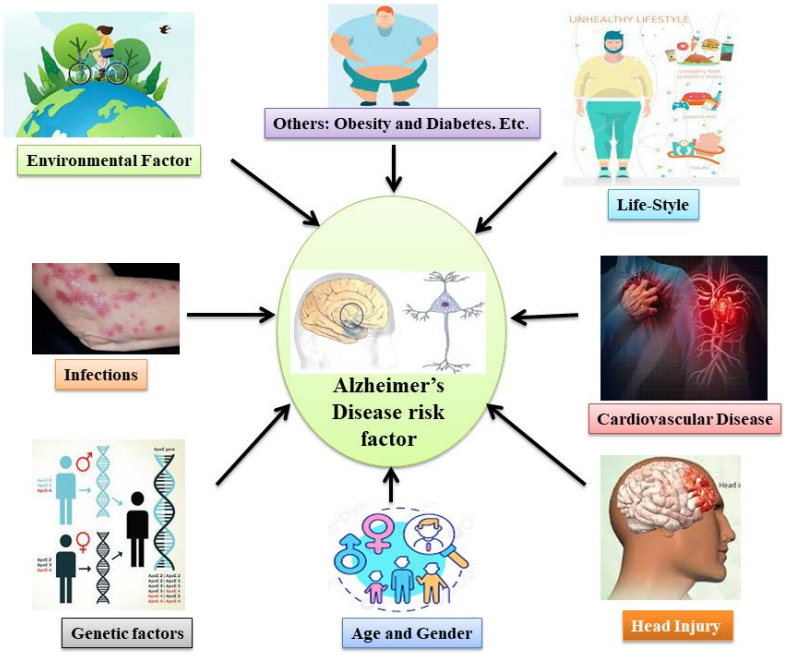

Fig.8: Risk factors for Alzheimer's disease(157).

- **Obesity and Diabetes**

Obesity is a phrase used to describe having too much body fat in humans as a result of ingesting more calories than they burn, and it may be calculated using the body mass index (BMI). Increased body obesity is linked to decreased brain blood supply, which increases cerebral ischemia, memory loss, and vascular dementia. Obesity, an unhealthy diet, and other factors can result in impaired glucose tolerance (IGT) or diabetes, which is characterized by hyperglycemia that damages peripheral tissues and blood vessels. Chronic hyperglycemia can cause cognitive impairment due to increased amyloid-beta buildup, oxidative stress, mitochondrial dysfunction, and neuroinflammation.Obesity is characterized by

increased pro-inflammatory cytokine releases from adipose tissue, which excite macrophages and lymphocytes and eventually contribute to local and systemic inflammation.Insulin resistance, hyperinsulinemia, and, as a result, hyperglycemia are all promoted by this inflammation.Obesity is a well-known risk factor for type 2 diabetes, CVDs, and cancer, all of which have been linked to dementia and Alzheimer's disease. Inflammation in the brain generates an increase in microglia, which leads to decreased synaptic plasticity and poor neurogenesis. Microglia have the ability to influence insulin receptor substrate 1 (IRS-1) and prevent intracellular insulin signalling, which is critical for neurological health. As a result, changes in insulin action can cause Aβ buildup and inhibit tau protein breakdown associated with AD(158–161).

- **Infections**

Chronic infections of the central nervous system (CNS) can result in the formation of A plaques and NFT, making them risk factors for Alzheimer's disease. Dr. Itzhaki's research identified herpes simplex virus (HSV-1) DNA among ApoE-4 allele carriers, explaining the elevated risk of acquiring Alzheimer's disease. HSV-1 can proliferate in the brain, activating the inflammatory response and increasing A deposition, causing in neuronal damage and the slow development of AD. Miklossy and Balin's findings, on the other hand, have demonstrated the involvement of chronic bacterial infections in Alzheimer's disease.For example, syphilitic dementia caused by spirochete bacteria (Treponema pallidum) accumulating in the cerebral cortex created lesions resembling neurofibrillary tangles, leading to catastrophic neurodegenerative illnesses. Furthermore, the Chlamydia pneumonia bacterium can cause late-onset Alzheimer's disease by activating astrocytes and cytotoxic microglia, disrupting calcium regulation and apoptosis, resulting in cognitive function impairment, and increasing the risk of Alzheimer's disease(162–164).

- **Genetics**

Over time, genetic variables were determined to play a significant influence in the development of AD. Most cases of EOAD are inherited in an autosomal dominant manner, and mutations in dominant genes such as Amyloid precursor protein (APP), Presenilin-1 (PSEN-1), Presenilin-2 (PSEN-2) and apolipoprotein E (ApoE) are associated with AD(165,166).

- **Cardiovascular Disease (CVDs)**

CVDs are recognized as a key risk factor for Alzheimer's disease, such as stroke, which is associated with an increased risk of dementia due to brain tissue loss, which intensifies the degenerative effect and effects amyloid and tau pathology. Atrial fibrillation can also result in embolisms, which can lead to stroke and a decline in memory and cognitive function. Furthermore, heart failure impairs the heart's pumping capacity, resulting in insufficient blood supply to the body and hypo-perfusion of the brain, which leads to hypoxia and neuronal injury.According to the coronary heart disease hypothesis, atherosclerosis, peripheral artery disease, hypo-perfusion, and emboli are all linked to an elevated risk of AD. Hypertension is related with artery wall thickening and lumen narrowing, which restrict cerebral blood flow, and in chronic situations, it may develop cerebral edoema, both of which are risk factors for AD and CVD. CVD is a controllable risk factor, and by concentrating on its association with Alzheimer's disease, a road to preventing and delaying the condition can be gained(167,168).

- **Age and Gender**

Age is the most powerful predictor of dementia. The prevalence of dementia rises dramatically in people over the age of 80, and it is higher in older women than in men. Alzheimer's disease (AD) doubles every four years in both men and women between the ages of 65 and 80, reaching a prevalence of 30% by the age of 80.Family background: Patients who have a first-degree relative with dementia are 10% to 30% more likely to get AD. Approximately 7% of cases with early onset are familial, with an autosomal dominant pattern of inheritance and penetrance. Dementia investigations in Swedish twin groups indicated no sex differences in the incidence of dementia or AD among initially intact participants followed longitudinally(169–172).

- **Head injury**

Mortimer et al's meta-analysis of seven case-control studies completed before 1991 provides the most convincing data to date in support of a link between head injury and Alzheimer's disease. The raw data for each case-control study in this study were obtained directly from the original authors. Mortimer et al found a relative risk of 1.82 (95% CI 1.26 to 2.67) for head injury with loss of consciousness. When corrected for a family history of dementia, education, and alcohol intake, the relative risk remained substantial but only for males (2.67, 95% CI 1.64 to 4.41) and not females (0.85, 95% CI 0.43 to 1.70)(173).Head injury with loss of consciousness: We were interested in severe head injuries that occur infrequently and are likely to have neurological consequences. As a result, we demanded that studies characterize head trauma in terms of the presence or absence of loss of consciousness. By omitting minor head traumas, research

should be less susceptible to recollection bias and less likely to discover a relationship that is simply a result of the dementia's prodrome. The period of unconsciousness was not limited in time(174).

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CONCLUSION AND FUTURE DIRECTION

Our review articles begin with an overview of Alzheimer's disease, including symptoms and indications. Alzheimer's disease biomarker, Alzheimer's disease nanotechnology treatment, Alzheimer's disease herbal drug, and Alzheimer's disease risk factors, and the conclusion of our review is that medicine does not cure completely and has harmful side effects on the body, while non-pharmacological treatment gives a good result but takes time and has no harmful effects on the human body.More randomized controlled trials on Alzheimer's treatment are needed. In the future, we want to conduct a preliminary investigation into Alzheimer's illness. In our location, we are doing a counselling-based research project to assess patient mental health and provide improved statistics on Alzheimer's disease and its treatment.

Table.1:Summary of patents on Alzheimer's Disease

Patent Number	Year	Disease	Inventor/Applicant/Country	Title of Invention	Ref.
US2020/0309789 A1	2020	Alzheimer's	Kazuhiko UCHIDA/MCBI INC/United States	Biomarkers for cognitiveDysfunction diseases and methodFor detecting cognitiveDysfunction disease using Biomarkers	(175)
WO2005/258940 A2	2005	Alzheimer's	Arumughamrasappa/A.Krishna/US	Immunogenic peptide carrier conjugates and methods of producing same	(176)
WO 2008/051599	2007	Alzheimer's	HUNG, David T. Redwood City/ Medivation Neurology, Inc. San Francisco /US	Combination therapies for treating Alzheimer's disease using dimebon and Donepezil	(177)
WO 2008/133274	2014	Alzheimer's	TAMURA, Yuusuke Osaka-shi Osaka/ Shionogi & Co.	Amino-dihydrothiazine derivatives substituted with cyclic groups	(178)
US2021/0095012 A1	2021	Alzheimer's	Yoshio Goshima/Yokohama City University/US	Anti - semaphorin 3A antibody and Treatment of Alzheimer's disease and inflammatory immune diseases Using same	(179)
US 7,640,062 B2	2009	Alzheimer's	Alon Shalev/US	Methods and systems for management of Alzheimer's disease	(180)
US 8,883,779 B2	2013	Alzheimer's	Moriyasu Masui/US	Oxazine derivatives and A Pharmaceutical composition forInhibiting bace1 containing them	(181)
US 8,895,548 B2	2014	Alzheimer's	Naotake Kobayashi/Shionogi & Co., Ltd./US	Pharmaceutical composition for treating Alzheimer's disease	(182)
US9,018,219 B2	2015	Alzheimer's	Moriyasu Masui/US	Fusedaminodihydropyrimidine derivative	(183)
US10 ,106 ,556 B2	2018	Alzheimer's	Shuhei ikeda/ Takeda Pharmaceutical Company limited/us	Heterocyclic compound	(184)

Table.2: Current status of clinical trials on Alzheimer's Disease.

S.no.	Drug	Mode of administration	Disease	Enrollment	Allocation/Intervention model/Masking	Official Title of the study	status	Clinical trial	Year
1.	**Aricept/ INM-176**	Interventional	Alzheimer's Disease	**280**	Randomized/Parallel Assignmen/Double (ParticipantInvestigator)	Probable Alzheimer Type Dementia Compare INM-176 1200~1600mg/Day With Donepezil 5~10mg/Day of Safety and Efficacy to Randomization, Multicenter, Double-blind, Double-dummy, Parallel Phase III Clinical Study	**Phase-3**	NCT01245530	2011
2.	Sargramostim GZ402664/Leukine/ Placebo/Florbetapir F18	Interventional	Alzheimer's Disease	0	Randomized/Parallel Assignmen/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	A Study Examining the Safety and Activity of Innate Immune System Stimulation WithLeukine® (Sargramostim) to Reduce Brain Amyloid Load in Patients With Mild Cognitive Impairment Due to Alzheimer's Disease	**Phase-2**	NCT02667496	2017
3.	SAR110894/Donepezil	Interventional	Alzheimer's Disease	**291**	Randomized/Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	A Multinational, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Study of the Effect on Cognitive Performance, Safety, and Tolerability of SAR110894D at the Doses of 0.5 mg, 2 mg, and 5 mg/Day for 24 Weeks in Patients With Mild to Moderate Alzheimer's Disease on Stable Donepezil Therapy	**Phase-2**	NCT01266525	2016
4.	Exercises with Nintendo Wii virtual reality device	Interventional	Alzheimer's Disease	**32**	Randomized/Parallel Assignment/None (Open Label)	The Effect of Virtual Reality Application on Balance and Gait Speed in Individuals With Alzheimer's Dementia	**NA**	NCT03928405	2019
5.	Innovative Medicines Initiative	Observational [Patient Registry]	Alzheimer's Disease	**2095**	**NA**	European Prevention of Alzheimer's Dementia (EPAD) Longitudinal Cohort Study (LCS)	**NA**	NCT02804789	2020

6.	ENA713	Interventional	Alzheimer's Disease	**121**	N/A//Single Group Assignment/None (Open Label)	A 52-week, Prospective, Multi-center, Open-label Study to Assess the Tolerability of Rivastigmine Before and After Switching From Oral Formulation to Transdermal Patch in Patients With Alzheimer's Dementia in a Controlled Titration Schedule	**Phase-4**	NCT01585272	2018
7.	CPC-201	Interventional	Alzheimer's Disease	**21**	N/A//Single Group Assignment/None (Open Label)	Safety and Tolerability of CPC-201 in Patients With Dementia of the Alzheimer's Type Long Term Extension Safety Study in Patients With Dementia of the Alzheimer's Type Who Completed Study CPC-001-07	**Phase-2**	NCT02434666	2017
8.	CT scan	Interventional	Alzheimer's Disease	**4**	N/A//Single Group Assignment/None (Open Label)	Low Dose Ionizing Radiation Using CT Scans as a Potential Therapy for Alzheimer's Dementia (LDIR-CT-AD) Trial: A Pilot Study	**NA**	NCT03597360	2022
9.	predictive value of a blood test	Interventional	Alzheimer's Disease	**2000**	Randomized/Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	Accuracy of Blood-based Biomarkers in Diagnosing Alzheimer's Disease in Clinical Practice	**NA**	NCT05187819	2022
10.	inpatient geriatric consultation team	Interventional	Alzheimer's Disease	**59**	N/A//Single Group Assignment/None (Open Label)	A Pilot Study of the Short-term Effects of an Inpatient Geriatric Consultation Team on Geriatric Syndrome Patients	**NA**	NCT03840759	2019
11.	Cilostazol/Placebo	Interventional	Alzheimer's Disease	**46**	Randomized/Parallel Assignment/Double (ParticipantInvestigator)	Cilostazol Augmentation Study In Dementia (CASID): A Randomized, Placebo-controlled Pilot Study to Compare the Efficacy Between Donepezil Monotherapy and Cilostazol Augmentation Therapy in Alzheimer's Disease Patients With Subcortical White Matter Hyperintensities	**Phase-4**	NCT01409564	2014
12.	Human	Intervent	Alzh	**9**	N/A/Single Group	Open-Label, Single-	**Ph**	NCT0	2

	Umbilical Cord Blood Derived-Mesenchymal Stem Cells	ional	eimer's Disease		Assignment/None (Open Label)	Center, Phase 1 Clinical Trial to Evaluate the Safety and the Efficacy of NEUROTSTEM®-AD in Patients With Dementia of the Alzheimer's Type	**ase-1**	12972 18	0 1 2
13.	Life story questionnaire	Interventional	Alzheimer's Disease	**60**	Randomized/ Parallel Assignment/ Double (Participant Outcomes Assessor)	Effects of the Life Story Questionnaire on Physical Therapy Participation in Patients With Dementia: A Randomized Control Trial	**NA**	NCT0 58272 76	2 0 2 3
14.	Psychosocial caregiver intervention	Interventional	Alzheimer's Disease	**6**	N/A/Single Group Assignment/None (Open Label)	Single Arm Study of Modified REACH-VA Alzheimer's Caregiver Intervention in Vietnam	**NA**	NCT0 31006 17	2 0 2 0
15.	Elbow movement	Observational	Alzheimer's Disease	**280**	Cohort	Understanding and Objectively Measuring Paratonia in Persons With Dementia: a Surface Electromyography Approach	**NA**	NCT0 56064 45	2 0 2 2
16.	memantine ER/ Placebo	Interventional	Alzheimer's Disease	**677**	Randomized/Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Memantine in Patients WithModerate-to-Severe Dementia of the Alzheimer's Type	**Phase-3**	NCT0 03221 53	2 0 1 0
17.	virtual reality	Interventional	Alzheimer's Disease	**30**	Randomized/Sequential Assignment/ None (Open Label)	Developing an Immersive Gamification Technology System (ImGTS) for the Management of Patients WithBehavioral and Psychological Symptoms of Dementia (Phase 1 Trial)	**NA**	NCT0 52651 82	2 0 2 3
18.	Resonator	Interventional	Alzheimer's Disease	**30**	Randomized/Parallel Assignment/Single (Participant)	A Randomized, Single-Blind, Placebo-Controlled Pilot Study to Evaluate the Safety and Efficacy of the Application of Magnetic Fields Using the Resonator for the Treatment of Alzheimer's Disease in Addition to Standard of Care	**NA**	NCT0 11953 89	2 0 1 1
19.	Intergenerational Music Program	Interventional	Alzheimer's	**22**	N/A/Single Group Assignment/None (Open Label)	Project Unmute: The Feasibility and Appropriateness of an	**NA**	NCT0 46450 17	2 0 2

			Disease			Intergenerational Music Program Delivered by Adolescents to Older Adults With Declining Cognition			2
20.	BR4002/BR4002-1	Interventional	Alzheimer's Disease	**18**	Randomized/Crossover Assignment/None (Open Label)	A Randomized, Open-label, Single-dose, Crossover Study to Evaluate the Pharmacokinetics and Safety/Tolerability of BR4002 Comparing to BR4002-1 in Healthy Volunteers	Phase-1	NCT04462029	2020
21.	This is not an intervention study	Observational	Alzheimer's Disease	**400000**	Cohort	Development and Validation of a Multivariable Dementia Risk Prediction Model in UK Adults Using Routinely Available Predictors	**NA**	NCT03943641	2022
22.	Bromocriptine/ Placebos	Interventional	Alzheimer's Disease	**8**	Randomized/Parallel Assignment/ Quadruple (ParticipantCareProviderInvestigatorOutcomes Assessor)	Double-Blind Comparative Trial and Open-Label Extension Trial to Investigate the Safety and Efficacy of TW-012R in Alzheimer's Disease With Presenilin 1 (PSEN1) Mutations	**Phase-1, 2**	NCT04413344	2022
23.	Standard Diet	Observational	Alzheimer's Disease	**60**	Case-Control	Ageing Gut Brain Interactions	**NA**	NCT03593941	2021
24.	Semaglutide/Placebo	Interventional	Alzheimer's Disease	**24**	Randomized/Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	A Randomised Double-blind Placebo-controlled Clinical Study Investigating the Effects of Semaglutides.c. Once-weekly Versus Placebo on Central and Peripheral Inflammation in Participants With Alzheimer's Disease	**Phase-3**	NCT05891496	2023
25.	NA	Observational	Alzheimer's Disease	**29**	Cohort	International Collaboration for Real-World Evidence in Alzheimer's Disease (ICARE AD)- A Prospective Real-World Observational Study of Aducanumab-avwa in Patients With Alzheimer's Disease in the US	**NA**	NCT05097131	2023
26.	Gantenerumab/	Intervent	Alzh	**24**	**NA**	A Phase III,	**Ph**	NCT0	2

	Placebo	ional	eimer's Disease			Multicenter, Randomized, Parallel-Group, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Gantenerumab in Participants at Risk for or at the Earliest Stages of Alzheimer's Disease	**ase-3**	5256134	023
27.	Gantenerumab/ Matching Placebo (Gantenerumab)	Interventional	Alzheimer's Disease	**220**	Randomized/Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	A Phase II/III Multicenter Randomized, Double-Blind, Placebo-Controlled, Two-part Adaptive Design, Platform Trial of Investigational Treatments for Primary Prevention of Disease Progression in Dominantly Inherited Alzheimer's Disease	**Phase-2**	NCT05552157	2023
28.	E2814/Lecanemab/Matching Placebo (E2814)	Interventional	Alzheimer's Disease	**168**	Randomized/Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	A Phase II/III Multicenter Randomized, Double-Blind, Placebo-Controlled Platform Trial of Potential Disease Modifying Therapies Utilizing Biomarker, Cognitive, and Clinical Endpoints in Dominantly Inherited Alzheimer's Disease	**Phase-2, 3**	NCT05269394	2023
29.	CNP520 50mg/CNP520 15mg/Matching placebo	Interventional	Alzheimer's Disease	**1145**	Randomized/Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	A Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of CNP520 in Participants at Risk for the Onset of Clinical Symptoms of Alzheimer's Disease (AD).	**Phase-2, 3**	NCT03131453	2021
30	RO7126209/Placebo	Interventional	Alzheimer's Disease	**120**	Randomized/Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	A Phase Ib/IIa, Randomized, Double Blind, Placebo-Controlled, Multiple Ascending Dose, Parallel-Group Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of	**Phase-2, 3**	NCT04639050	2023

						RO7126209 Following Intravenous Infusion in Patients With Prodromal or Mild to Moderate Alzheimer's Disease			
31.	Gantenerumab/ Solanezumab/ Matching Placebo (Gantenerumab)/Matching Placebo (Solanezumab)	Interventional	Alzheimer's Disease	**194**	Randomized/Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	A Phase II/III Randomized, Double-Blind, Placebo-Controlled, Cognitive Endpoint, Multi-Center Study of Potential Disease Modifying Therapies in Individuals at Risk for and With Dominantly Inherited Alzheimer's Disease	**Phase-2, 3**	NCT04623242	2022
32.	Liraglutide/ non-active study drug	Interventional	Alzheimer's Disease	**34**	Randomized/Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	Neurodegenerative Changes in Alzheimer's Disease: Identifying Potential Effects of Liraglutide on Degenerative Changes	**NA**	NCT01469351	2013
33.	CAD106 Immunotherapy/ Placebo to CAD106/CNP520	Interventional	Alzheimer's Disease	**480**	Randomized/Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	A Randomized, Double-blind, Placebo-controlled, Two-cohort, Parallel Group Study to Evaluate the Efficacy of CAD106 and CNP520 in Participants at Risk for the Onset of Clinical Symptoms of Alzheimer's Disease.	**Phase-2, 3**	NCT02565511	2021
34.	Neurostar repetitive transcranial magnetic stimulator	Interventional	Alzheimer's Disease	**20**	Randomized/Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	Repetitive Transcranial Magnetic Stimulation for Apathy in Alzheimer's Dementia	**Phase-4**	NCT02190084	2019
35.	123-I MNI-187 Injection and Imaging Procedures	Interventional	Alzheimer's Disease	**30**	Non-Randomized/ Single Group Assignment/ None (Open Label)	Evaluation of [123I] MNI-187 and SPECT as a Marker of Beta-amyloid Protein Deposition in Subjects With Alzheimer Disease in Comparison to Healthy Subjects	**Phase-1**	NCT00456417	2019
36.	Evaluation	Observational	Alzheimer's Disease	**50**	**NA**	Comparison of Dual Assignment, Cadence, and Gait Speed in Alzheimer's Dementia and Healthy Geriatric Individuals	**NA**	NCT05767580	2023
37.	[123-I] AV-83 Injection and	Interventional	Alzheime	**30**	Non-Randomized/ Single Group	Evaluation of [123I] AV83 and SPECT as a	**Phas**	NCT00448720	20

	Imaging Procedures		r's Disease		Assignment/ None (Open Label)	Marker of Beta-Amyloid Protein Deposition in Subjects With Alzheimer Disease in Comparison to Healthy Subjects	**e-1**	99	08
38.	NA	Observational	Alzheimer's Disease	**40000**	**NA**	A Multi-center Longitudinal Cohort Study of Familial Alzheimer's Disease in China	**NA**	NCT03657732	2022
39.	NA	Observational	Alzheimer's Disease	**250**	**Cohort**	Modelling Tau Deposition and Distribution From Diffusion Tensor Imaging With Generative Adversarial Network for Alzheimer's Disease Diagnosis	**NA**	NCT05020626	2023
40.	Florbetapir F18	Interventional	Alzheimer's Disease	**96**	N/A/Single Group Assignment/Single (Outcomes Assessor)	The Feasibility and Reliability of Utilizing Commercially Available Quantitative Analysis Software as an Adjunct to the Clinical Qualitative Interpretation of Amyvid Brain Scans	**Phase-4**	NCT01946243	2015

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