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Review Article

Biomedicines: Potential Tools for Managing And Treating Alzheimer's Disease

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ABSTRACT

Background: Alzheimer's disease[AD] Is a type of dementia as it affects a most of a people in world wide .As neurons are affected first it causes a progressive memory loss and cognitive function ,further causing visual and language deficiencies which results in aggression, depression and apathy.It affects life style, diet, environment .The FDA approved medicine, which provides sympathomimetic relief but, it produces some adverse affects .Many natural product like Centella asiatica which is a Ayurvedic plant which contain phytochemicals like alkaloids, flavonoids ,tannins, terpenoids, saponin, steroids, carbohydrates ,and cardiac glycosides in its aqueous extract. Some risk of AD is due to genetics .However some acquired factors like CVD, diabetes, hypertension, obesity, and dyslipidemia increase risk of AD development. Objectives: Some researchers with the help of antibodies thought to remove amyloid plaques , and by using a gene therapy to remove defective gene and then biomarkers will minimize side effects and enhance a effectiveness and by modifying health , management of Alzheimer's disease will takes place. Discussion: A immune therapy to target a amyloid beta and tau protein and with a help of biomarkers to detect early signs and symptoms by modifying life style a risk factor can be controlled. Conclusion: In conclusion, the landscape of tools for managing and treating Alzheimer's disease is evolving rapidly. While no definitive cure exists, a combination of pharmacological interventions, cognitive therapies, and lifestyle adjustments shows promise .Emerging technologies like artificial intelligence for early diagnosis and personalized treatment plans offer hope for more effective approaches, Collaborative efforts between health care professionals ,researchers, and technology developers are crucial in advancing our understanding and enhancing the tool kit for Alzheimer's management. Continued research and innovation solutions are essential for improving the quality of life for individuals affected by this challenging condition.

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INTRODUCTION

Alzheimer's disease(AD) is a type of a neuro-degenerative chronic disorder, which is a non-linear and multifactorial disease which affects individual's life.[1] The main causes is due to accumulation of amyloid beta and protein tau ,neurofibrillary tangles and senile plaques ,which is a composed of phosphorylated protein which is an intra neuronal findings(.Accumulation of beta amyloid protein occur in capillaries walls ,arteries and arterioles causing amyloid cerebral angiopathy, leading to degeneration of vascular wall which leads to worsening of blood flow ,further it causes epigenetic changes[2],oxidative stress, glutamate excitotoxicity ,inflammation and cholinergic system dysfunction which leads irreversible loss of synapse and neuron and visuospatial disability[3].It is important to note that there is a subgroup of AD patients which don't present typically a amnestic picture ,manifesting non-amnesting deficits from onset of symptoms .In initial stage AD show some changes, but not the major symptoms is the cognitive impairment stages which include memory loss and other impairment in cognitive[4].Dementia ,which is a last stage of AD affects individual's life[5].Hippocampus is a first affected part and is a first affected part and it further affect the entorhinal cortex ,it later affects cerebral cortex as hippocampus is a crucial part of a brain which is responsible for AD as a time passes more neurons was damaged and brain starts to shrink [6], some behavioral changes and deficient of a language, reasoning and disorientation and increased anxiety ,memory loss aggregation and reinforces the diagnosis ,definite diagnosis of disease is carried out through only by a postmortem examination[7].

EPIDEMOLOGY

It is estimated that more than 47 million people was affected with dementia at 2018,it is a 5th leading causes of mortality .In France ,recently 1.1 million people was affected with AD ,with occurrence of 225,000 new patient every year[8] .Aging is a strongest risk factor for AD ,it was estimated that at 2050 there will be more than 131 million will get affected .Prevance was estimated at 10% for individual over 65 years and 40% for those over a period of a 80 years[9].

RISK FACTORS AND CAUSES

The main cause is due to accumulation of beta amyloid and protein tau .The dominantly inherited familial AD(FAD) can be caused by mutations in amyloid precursor protein (APP), presenilin (PESN1) or (PESN2) genes ,early onset alzheimer's disease(EOAD) was affected by most of people of age below65 years[10].

GENETICS

Although genetic risk factors have been identified most generally apolipoprotein E gene(APOE) is a gene which cause a AD in fact ,in 202 there are 31 new gene was identified which cause AD[11].The most important gene APOE-e4 has strongest impact on AD ,whereas late-form of AD is mainly associated with a polymorphism in APOE gene .Individual having a single copy of APOE4 polymorphism have odd ratio for AD .APOE-e4 is the first risk gene identified[12].APOE is a blue print of protein tau that transports cholesterol in risk the risk as compared to e3 form,e3 allele have neutral effect in AD. The e4 allele in heterozygosity form have 3-fold increase in risk for AD and then e4 allele have homozygosity form as 12-fold increase in risk for AD[13].APOE2 and APOE3 is useful in clearing the peptide and thereby reducing its deposition in brain APOE is useful in neurons development as apoE2,apoE3 have better effect than apoE4,the protease-generated apoE4 have greater toxic effect which cause neural injury, the triggering receptor present on myeloid cells 2(TERM2) gene have greater risk APOE-e4 with a risk of AD is common in white individuals, the genetic factor ATP-binding cassette transporter (ABCA7)protein cause AD[14].

TRISOMY IN DOWN SYNDROME

In down syndrome,an individual with 3 copies of chromosome 21 (known as trisomy 21) have increase risk of AD. Chromosome 21 gene encode for production of amyloid precursor protein (APP) in which the people with AD cut into beta- amyloid fragment cause accumulation of plaques and having extra copies of chromosome 21 may increase production of beta amyloid fragment in brain[15].The person with down syndrome will exhibit symptoms of AD ,the life expectancy for people have been developed in last 70 years ,is noted with corresponds to growing population of adult. Dementia is a main cause of death.Care for down syndrome and dementia is challenging due to visual intellectual disability, cognitive and communication impairments which affects people[16].

PREVALNCE

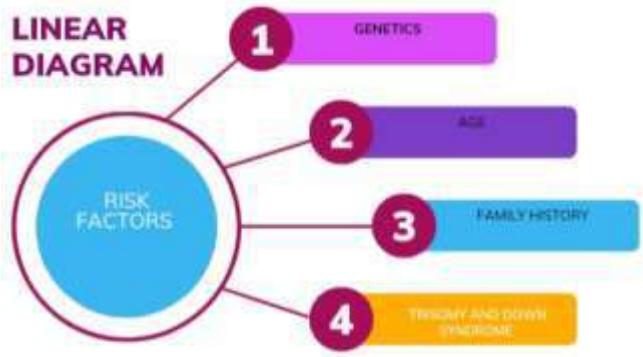
Down syndrome people develop AD in early stage at the age of 40 ,the level of beta amyloid plaques and tau protein is increased on the basis of NATIONAL DOWN SYNDROME SOCIETY about 30% of people at the age of 50s have down syndrome and50% of people [17].

AGE

The greatest known risk factor for Alzheimer's and other dementia is due to increasing age. Most individuals with this disease are of 65 years and older the risk will be doubles after five years and after that at the age of 85 the risk will be reaches to one third[18].

FAMILY HISTORY

A family history of AD not necessary for a individual to develop a disease, researchers have shown that an individual with brother ,sister (first-degree relative) and parent with AD are more likely to develop disease[19].The risk will increased ,if more than one family member has this disorder, those individual have more than one first-degree relative with AD are having higher risk[20] ,some researchers have found that parent with dementia increases risk independent of genetic factor such as APOE4 some factor such as food habits and physical activity may play a role in AD[21].



PATHOPHYSIOLOGY

As the brain has millions of neurons with axon, dendrite and synapse ,it helps to communicate between one neuron to another neuron will takes place which is used to carry out metabolism and repair themselves[23].Neuronal loss and are of pathology may be seen particularly in hippocampus ,amygdala, entorhinal cortex and cortical association areas of frontal, temporal and parietal cortices ,but also associated with subcortical nuclei[24].The accretion of tau protein correlates very closely with cognitive decline and brain atrophy, including hippocampal atrophy[25]. There mainly 4 changes in brain structure shows AD

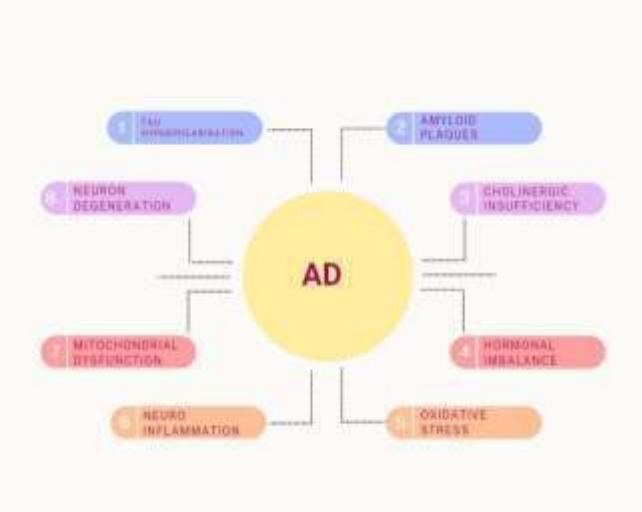
- Cortical atrophy
- Presence of neurofibrillary tangles(NFT's)
- Degradation of cholinergic and other neurons
- Beta Amyloid protein and apolipoprotein E are two proteins that contribute to genesis of NFT's and NP's are 2 features of AD's lesion[25]

The 2 significant lesions in AD's disease. They are:

Neuro Fibrillary Tangles (NFT's)	Neuritic Plaque(NPs)
A tau protein changes can cause collapse and clumping which results in neurofibrillary tangles.	Deposition of a beta amyloid can cause accumulation in brain between neuron's.
They are located in intra-cellularly within cytoplasm of neurons.	Plaques are compressed of core of beta amyloid proteins surrounded by axon and dendrite projections of neurons.
These are present in normal brain mainly in hippocampus, amygdala cerebral cortex.	They are lesions which are present in brain and cerebral cortex.
Due to the NFT it disturbs cell structure and its functions and results in death.	They interfere with neural transmission pathway.
It mainly accumulates in important part of brain before spread into other regions.[26]	It causes direct neurotoxicity[27].

Degeneration of cholinergic neuro transmission

They are present in important of brain such as amygdale, hippocampus which are important for learning, memory but in AD it will leads to blockade of cholinergic neurotransmission which ultimately causes memory loss[28].



RELATION BETWEEN GUT MICROBIOTA & AD

Gut microbiota can cause progression of AD through pro-inflammatory mediators ,neurotransmitters and metaolites to promote accumulation ,aggregation of hyper phosphorylated tau, and chronic neuro inflammation[29].The gut microbiota further affects brain health by the secretion of short-chain fatty acid toxins which modulate gut permeability and numerous immune functions ,the inflammation associated bacteria like Escherichia and Shigella bacterial taxa was found to be a reason for AD[30].Vogt.et.al .has observed a significant decrease in species diversity of intestinal flora from AD patient with decreased abudance of Firmmicutes and Bacilli and overrepresentation of Bacteriosidesgenus ,the age related changes in gut microbiota were compiled with amyloid plaque accumulation and impairment in learning, thinking and memory[31].The gut –brain axis (GBA) which is a signaling pathway between gastro intestinal (GI) tract and CNS which have bidirectional communication .GBA is used to monitor intestinal functions as well as it links immune and neuro-endocrine mediators[32].Through this communication brain affects gut ,sensory ,movement and secretory functions ,so the signal from gut affects brain function. They affect the vagus nerve, but also by the secretion of cortisol by HPA axis in case of stress which affects intestinal motility and mucus production will causes changes in composition of gut microbiota which in turn affects CNS[33] .As the normal microbiota is useful in host nutrient metabolism, maintenance of structural integrity of gut mucosal and in metabolism of host nutrient and useful in modulation of immune system and protection against the pathogen ,by the production of protein by certain intestinal bacteria which is identified in the blood of patients will modify the changes in immune and nervous system and causes the diseases[34].The Alzheimer's was linked to

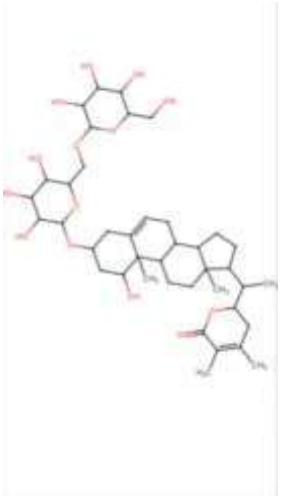
pneumonia ,oral herpes and with the bacteria Spirochete(a type which causes lyme diseases and gum diseases[35].Using PET diagnosis we can measures amyloid deposition and their amount present in blood are the various inflammation markers. Probiotics are one of the preventative measures against AD, the selected bacterial strains is known to slow down the progression of AD[36].

PLANTS USED IN TREATING AD

Withania somnifera

It is a well- known as a Ashwagandha, which is belong to Solanaceae family and it is a neuroprotective plant, it is a adoptogenic Ayurvedic medicines, it is the one of the most prominent herbs which is used as a brain rejuvenator for AD, it is used as a nerve tonic[37].In vivo phase, withanolide A inhibited A beta (25-35) administered rats oral administration of withanoside IV induces degeneration of axons, dendrites, and synapses in hippocampus ,cerebral cortex which helpful in restoration of memory and to improve cognitive function[38].In mice methanol extract of W. somnifera helps to reduce amyloid plaques as Ashwagandha is related to liver protein, it will enters the blood system and reduces accumulation of amyloid plaques in brain[39].As Ashwagandha contain vitamin E&C it is a more potent anti-oxidant which is acts as a scavangers of free radicals and helpful in progression of AD[40].By the administration of W. somnifera it increases the Ach content and choline acetyl transferase activity (AchE) which is a neurotransmitter helps to restore memory and cognition activity. Ashwagandha acts as aAchE booster and increase energy level of patient and helps to increase the numerous production of brain cells and also acts as a immune booster, as Ayurvedha came in progression in 10 BCE ,the chemical constituents of W.somnifera are 40 withanolides,12 alkaloides and many sitoindosides and also with a help of Ashwangandha it is also used in improvement in executive function .information-processing speed and sustained attention.The role of Ashwagandha further progressed in improving executive function in the people with spinal cord injury(SCI) and mild cognitive impairment (MCI)[41].

WITHANOSIDE

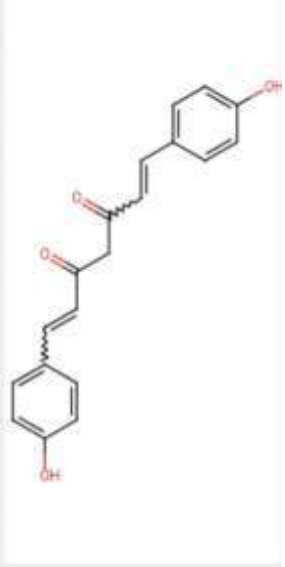


Curcuman longa

It is consists of dried as well as fresh “Rhizomes” of the plant Curcuma longa belongs to family Zingiberaceae, it is also known as a Haldi which is a ayurvedic medicines also known as a “cleanser of the body” the chemical constituents consists of a 50-60% of curcumin,2-7% of essential oil with high content of bisabolane derivatives and also contain Desmethoxycurcumin(DMC), Bisdesmethoxycurcumin (BDMC),common phytosterols, ar-tumerone, Zingiberene fatty acids and polysaccharides which also cultivated under propagation process[42] and Curcumin has used as a antioxidant, the BDMC and DMC are responsible of inhibiting formation of A beta protein because of its low bioavailability, rapid GIT metabolism and poor BBB penetration several analogue of curcumin was studied to treat AD the curcumin reduces accumulation of beta amyloid plaques and also reduces phospholipase and cyclooxygenase mediator which helps in improving memory and cognitive function as curcumin helps in reversing physiological damage by disruption of existing plaques and restoration of

distorted neurites, and also because of lipophilic nature of curcumin it crosses BBB and binds to plaques as a result the plaque accumulation get reduced .As curcumin has a greater binding affinity for copper, iron which acts as a protective agent against AD as it is induced a iron mediated damage[43].

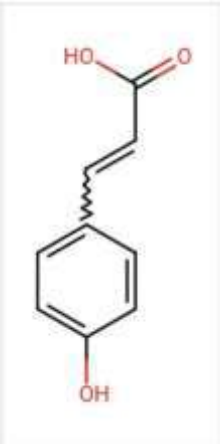
BISDESMETHOXY CURCUMIN(BDMC)



Convolulus pluricaulis

It is also known as Shankhpushpi as a ayurvedic family it is used to improve memory and to treat brain related ailments. The chemical constituents consists of triterepenoids, flavonolglycosides, steroid, coumarines, alkaloids, sitosterol, hydroxylcinnamic acid, octacosanol, tetracosane and anthocyanins which have memory-enhancing properties. Cholinergic and glutamatergic signaling have been enhanced by a group of nutraceuticals called racetams and also modulates production of adrenaline and cortisol. C. pluricaulis is acts as a brain tonic tranquilizers and calms the nerve by regulating stress hormone, by the significant increase in Ach activity and the activation of a acetyl choline esterase the learning and memory functions has enhanced, the extracts of Shankhpushpi with ethanolic extract enhance memory and neuritic growth, the herbs has not been evaluated clinically to test whether it can prevent dementia[44].

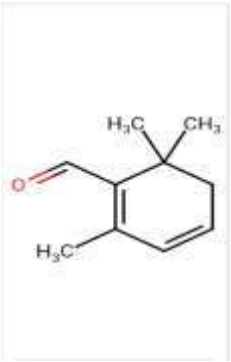
HYDROXYLCINNAMIC ACID



Crocus sativus

It is also known as a Saffron which is also have a neuroprotective effect and used as cognitive impairment in patients with AD and as a result researchers compare saffron extract with cholinesterase inhibitor donepezil is used to treat mild to moderate AD as it inhibit the aggregation and deposition of beta-amyloid plaques[45].The saffron is also extract with memantine in reducing cognitive defects and also helps in reducing in MCI ,the chemical constituents consists of 63% sugars (comprising starch, gums, reducible sugars, dextrins, pectin, and pentosans) 12% protein,10% moisture ,5% crude fibres, terpenes, terpene alcohol and their ester[46].

SAFRANAL



Hericium erinaceus

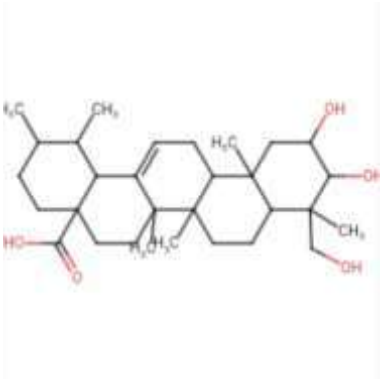
It is also known as a Lion's mane (Lm) as it is has a neuroprotective properties,and helpful in visual recognition memory and the oral administration of

H. erinaceus increases expression of NGF mRNA in hippocampus and in prevention of spatial, short-term memory. HEM increases serum and hypothalamic concentrations of Ach and choline acetyltransferase in a dose dependent manner , as Lm extracts has been results in reducing accumulation of A beta plaque and elevation of(Nerve growth factor) NGF levels. And also Lm helps in increasing neurogenesis ,Lm is a safe herb and well-tolerated one which is used in management of AD[47].

Centella asiatica

It is known as a mandukaparni in ayurvedic medicine system of india and also known as a Gotu kola(GK) which belongs to umbeliferae family ,the chemical constituents consists of Asiatic acid ,asiaticosides, triterepenes ,sapogenisis, glycosides, madecassia acid ,it helps in preventing accumulation of amyloid plaque ahd results in curing AD[48],GK as a medicinal herb which is belongs to apiaceae family also as used as a revitalization of nerve and brain cell and GK also used in blocking H2O2 induced cell death and results in decreasing free radical concentration and GK has significant cognitive-enhancing activity in a scopolamine-induced memory memory impairment model as scopolamine induces transient memory deficits similar to early AD the cognitive enhancing effect is due to increased choline acetyltransferase activity which results in Ach synthesis GK is also applied for fighting mental and physical exhaustion ,the extracts of plant have a in-vivo effects against many neurological disorders ,centella asiatica has also been proven to improve memory performance .GK also have mitigating age-related decline in mood swing and cognitive function in healthy elderly, GK are also focused molecular mechanism of neuroprotective[49].

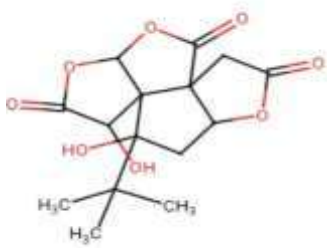
ASIATIC ACID



Gingko biloba

It is belongs to Gingkgoacaeae family ,the gingko biloba leaves contains 24% of flavone glycosides which is consists of quercetin, kaempferol and iso rhamnetin and terpenes lactones consists of A,B and C ginkgolides and bilobalides gingko biloba is useful in treating memory loss ,headache and loss of consciousness and also in abnormalities of blood circulation, it is also limited by only being of use in early stages of AD, once patients have progressed beyind this condition the herbs has not been found to have any beneficial effects Gb extracts has a inhibiting action on beta-amyloid peptide aggregation in AD patients and NO – induced toxicity treatment of mice with Gb extracts enhances the short term memory and in young and old rats to induce memory retention as Gb is an effective cholinesterase inhibitors and in inhibition of membrane lipid peroxidation[50],the flavonoid fractions of G.biloba extracts acts as a free radical scavengers and have cholinergic and neuroprotective activity in treating AD, free circulating cholesterol has also been affect APP processing and amyloidogenesis Yao et al have show that the level of circulating free cholestrol were lowered and the production of beta APP and A beta peptides were also inhibited[51].

BILOBALIDES



GENE THERAPY

AD was coming under the phase 1 clinical trials with nerve growth factor (NGF)in humans was initiated ,but it is too large to cross BBB, as familial AD is an autosomal dominant disorder which is occur at age of onset of before 65 years, although NGF infusions will results in weight loss , as NGF administration results in more persistent effect than AChE inhibitors[52].The present trials was attempted to protect the cholinergic neuron from degeneration as IV infusion of NGF prevents lesion as it also elevate a choline acetyl transferase (ChAT) function ,the trials have also been showed improved effect in cognitive function as NGF has results in increased in both lesion induced and age related spontaneous degeneration of cholinergic neuron, but if fibroblast deemed the patient will receive a inter cerebral injection but when neuron have been undergone atrophy will results in AD. Synapsin-Caveolin -1 is used in preserving a neuronal and synaptic morphology and helps in prevent AD[53].

ANTIOXIDANT THERAPY

MOLECULAR HYDROGEN AS AN ANTIOXIDANT IN AD

The primary mechanism by which molecular hydrogen acts as an antioxidant is by selectively reacting with and neutralizing harmful hydroxyl radicals (OH), which are highly reactive and cause damage to biomolecules like nucleic acid, proteins and lipids. By targeting these destructive hydroxyl radicals, molecular hydrogen to mitigate the oxidative stress that contributes to the development and progression of neurodegenerative disease like AD. Hydrogen ion ability to penetrate cell membrane and diffuse into cellular organelles, such as mitochondria and the nucleus[54]. This means that it can effectively reach the sites where the free radicals are generated and neutralize them, providing cyto protective benefits.

They are multiple methods of administering molecular hydrogen, including

- Inhalation
- Ingesting hydrogen- rich water
- Injecting hydrogen-rich saline
- Bathing in hydrogen- rich water or
- Increasing the production of intestinal hydrogen through bacterial action on undigestible carbohydrates.

These diverse delivery methods offer flexibility in utilizing molecular hydrogen as a therapeutic agent. Research on molecular hydrogen has increasing survival and life span in certain animal models and reduce neurotoxicity induced by amyloid beta (Aβ) in neuronal cells[55].

EBSELEN ANTIOXIDANT EFFECT IN AD

Ebselen, which contains selenium (Se), has been studied for its antioxidant properties and ability to mitigate the impacts of AD pathology. It exerts its neuroprotective effects by enhancing the activity of glutathione peroxidase (GPx) and superoxide dismutase (SOD), both of which are important enzymes in combating oxidative stress. Ebselen also reduces the levels of oligomeric amyloid-beta (Aβ) in the brain, a key hallmark of AD, by modulating the expression of proteins involved in Aβ synthesis[56]. In addition to ebselen, other antioxidant compounds have shown promise in animal models of AD when used alone or in combination with other drugs or antioxidants. Some examples of such combinations include ebselen with donepezil, lipoic acid with donepezil, ferulic acid with tacrine, and polyphenolic hybrids. These combinations likely work synergistically to

provide enhanced neuroprotection compared to using a single antioxidant compound[57].

Researchers are now looking into the neuroprotective effects of antioxidants in human trials. To be effective in humans, antioxidant drug compounds need to be able to pass through the BBB. This can be achieved by ensuring the compounds are lipid-soluble and small enough to penetrate the BBB. Additionally, researchers are exploring the use of carrier molecules that can transport the antioxidants from the bloodstream into the brain without causing toxicity[58].

RESVERATROL ANTIOXIDANT ROLE IN AD

Resveratrol is a polyphenolic compound that has gained significant attention for its potential as an antioxidant treatment for Alzheimer's disease (AD). As a potent stilbene antioxidant, it has been investigated for its safety, tolerability, and efficacy in impacting AD-related biomarkers[59].

A pilot study involving 39 patients with mild to moderate AD found that low-dose resveratrol (5 mg) was well-tolerated and as safe as a placebo when administered in combination with 5 mg dextrose and 5 mg malate twice daily for one year. This initial study provided encouraging results regarding the safety of resveratrol in AD patients.

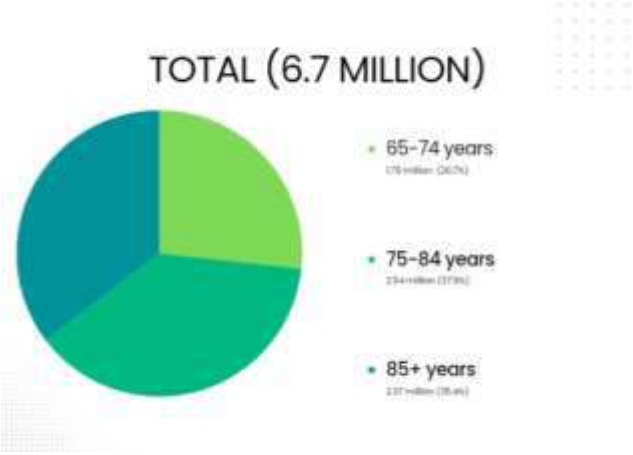
To further assess the potential benefits of resveratrol, a larger study was conducted with 119 patients with mild to moderate AD. In this study, the patients received up to 1 mg of resveratrol twice daily or a placebo for 52 weeks[60]. The results of this study demonstrated several positive effects of resveratrol:

1. Decreased CSF biomarkers: Resveratrol was found to have an impact on cerebrospinal fluid (CSF) biomarkers associated with AD. These biomarkers can provide valuable insights into the progression of the disease and its underlying mechanisms[61].

2. Modulated neuro-inflammation: Chronic inflammation in the brain is believed to play a role in the development and progression of AD. Resveratrol showed the ability to modulate neuro-inflammation, which could be beneficial for slowing down the neurodegenerative processes[62].

3. Induced adaptive immunity: Adaptive immunity refers to the body's ability to mount specific immune responses to target harmful substances. Resveratrol was found to induce adaptive immunity, suggesting a potential mechanism by which it may support the brain's defense against AD-related pathology[63]. While these findings are promising, it's important to note that resveratrol is just one of the many polyphenolic compounds being explored for potential therapeutic benefits in AD. As research continues, scientists are also investigating other antioxidants and their combinations to identify the most effective neuroprotective strategies for AD treatment.

PREVALANCE OF ALZHEIMER'S AND OTHER DEMENTIA



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