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Different Molecular Targets and Its Significant Role in Alzheimer's Disease: A Review

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Abstract

Alzheimer's disease is a severe neurodegenerative brain illness that affects the majority of the older population. Alzheimer's disease has become a substantial public health problem due to increased life expectancy in the general population and a better understanding of the disease's socioeconomic effects. This review explores the cholinergic theory, amyloid plaque formation, tau protein hyperphosphorylation, neuroinflammation pathway, oxidative stress, mitochondrial dysfunction, genetic aetiology, infectious pathways, and environmental factors in Alzheimer's disease. Physical and neurological tests, which include intelligence, muscle tone and strength, vision and hearing, and communication, are used to diagnose Alzheimer's disease. In order to make an early diagnosis, brain imaging techniques such as MRI and CT are used. Inflammatory biomarkers like IL-1, IL-6, TNF- α, and TGF- β are all computed in blood testing. The activity of acetylcholinesterase and the concentration of neurotransmitter acetylcholine are measured using a biochemical probe. There is no definite cure, although symptomatic treatment includes cholinesterase inhibitors such as Tacrine, Donepezil, and Rivastigmine, as well as NMDA antagonists such as Memantine are available. For better efficacy, combination therapy such as cholinesterase inhibitors with antioxidants and a combination of hybrid inhibitors has become preferred. Current research focuses on establishing various causes of disease and generating more effective, target-oriented pharmaceutical treatments.

Keywords
Acetylcholine, B-Amyloidal Plaque, Hyperphosphorylation of Tau, Proinflammatory Cytokines, Oxidative Stress, Cholinesterase Inhibitors.

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Introduction

Alois Alzheimer, a German psychiatrist, discovered the initial instance of Alzheimer's disease, which he named after himself, in 1901. Auguste D, a fifty-year-old woman with Alzheimer's disease, was identified and his case was followed till she died in 1906. Eleven more incidences of Alzheimer's disease were documented over the next five years. As a subtype of senile dementia, he included Alzheimer's disease, also known as presenile dementia by Kraepelin. Alzheimer's disease is only diagnosed in individuals among the ages of 45 and 65 who had dementia symptoms throughout the twentieth century. Presenile and senile dementia have the same clinical and pathological symptoms. However, the authors went on to explain that this did not rule out the possibility of various explanations. This finally led to an Alzheimer's disease diagnosis, regardless of age. For a while, the term senile dementia or Alzheimer's dementia was used to characterise the condition in those over the age of 65. Alzheimer's disease is strenuous to detect in its early stages. When cognitive impairment interferes with daily activities, a conclusive diagnosis is generally made. The symptoms will proceed from moderate cognitive issues, for instance, memory loss, to increasingly severe cognitive and non-cognitive disorders, obliterating any prospect of independent living, particularly in the late stages of disease. A reduced chance of survival is associated with escalated severity of cognitive impairment, poorer functional levels, a history of falls, and anomalies in the neurological test[1].

Alzheimer's disease is a chronic neurodegenerative illness characterised via increased neuronal cell death and neuronal dysfunction for which only symptomatic therapies are available currently[2]. Alzheimer's disease is an enduring brain disorder marked by cholinergic transmission impairment, amyloid plaque configuration, tau hyperphosphorylation, neurofibrillary tangles (NFT), oxidative stress, mitochondrial dysfunction, and increased proinflammatory biomarkers such as cytokines and interleukins[3]. It is one of the stereotypical causes of dementia, and accounts for 60 to 80% of cases. Millions of individuals in the United States endure from Alzheimer's disease or other dementias. As numerous individuals aged 65 and up in the United States grows, number of individuals with AD increased. The number and proportions of Americans aged 65 and older are expected to quickly increase in the next years, rising from 58 million in 2021 to 88 million by 2050[4]. The inability to recall recent events is a universal symptom of AD. Language difficulty, disorientation, mood swings, behavioural abnormalities, and a lack of self-motivation are some of the symptoms that develop as the condition progresses[5.] Average patient with Alzheimer's disease has a life expectancy of nine to ten years. However, a history of comorbidities was linked to a lower chance of survival and a higher risk of mortality. Other complicating factors, such as heart disease, diabetes, or a history of alcohol abuse, have also been related to a shortened lifespan[6].Neuropsychological testing can be used to evaluate whether or not someone has dementia. A physical examination can assist in determining the cause of dementia. Focal neurologic abnormalities, for example, may indicate a stroke. Structure changes in brain, such as localised atrophy, infarcts, and tumours, may be detected via brain scanning rather than physical examination. Neurofibrillary tangles (NFTs), which are embodied in paired helical filaments (PHFs) inclusive of microtubule-associated protein tau and accumulate in neuronal perikarya, and extracellular amyloid deposits in type of diffused neuritic senile plaques containing amyloid peptide, are the two most prominent neuropathological changes that associateamidinverdict of AD. NFTs, which are made up of bundles of PHFs, may be easily detected by antibodies that recognise the microtubule-related protein tau in Alzheimer's disease. Tau is hyperphosphorylated in autopsy-derived AD brains, with over 30 phosphorylation sites in PHF-tau protein. In atypical dementia patients, for instance, those with inception younger than 65 years, speedy symptom onset, and mutilation in manifold cognitive domains excluding not interrupte dreminiscence, further testing using CSF fluid tests or genetic testing may be undertaken. Patients should receive primary care to recognise and monitor disease, as they may confront a variety of diagnostic and therapeutic issues. This assists in the premature revealing and verdict of AD, elicits symptomatic pharmaceutical remedies and psychosocial support[7].

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Alzheimer's and the Brain

The hippocampus area of brain, which is primarily responsible for learning and memory, is the primary target of Alzheimer's disease. The dentate gyrus (DG), comuammonis 3 (CA3), and comuammonis 1 (CA1) are the three subregions of the hippocampus. Reduction of synaptic strength in DG areas causes memory impairment in older people. In older people, the firing of CA3 brain cells is frequently high. In mice, CA1 area is also linked to age-related memory degradation, although another theory is there, which is due to an increase in the number of silent synapses (no excitatory glutamatergic AMPA receptors) and calcium signals, which results in a long-lasting excitation signal. CA1 area is the most vulnerable to Alzheimer's disease[8].

Stages of Alzheimer's Disease

Alzheimer's disease has three stages:
Early stage Alzheimer's
Middle stage Alzheimer's
Late stage Alzheimer's

Early Stage Alzheimer's (Mild)

The most prevalent symptom is short-term memory loss, which causes difficulties in remembering recent events. Language, executive functioning, perception, apraxia, elevated anxiety, and difficulties in handling money and goods are more prominent.

Middle Stage Alzheimer's (Moderate)

Speech issues resulting from progressive deterioration, increased confusion, hallucinations, delusions, and paranoia are the symptoms.

Later Stage Alzheimer's (Severe)

Communication difficulties, loss of weight, sleeping time, and seizures.

Epidemiology

Dementia caused by Alzheimer's disease is a growing problem for the elderly in both developed and developing countries. It will be difficult for individuals to operate effectively in the community as a result of this. Alzheimer's disease is expected to affect 690 million individuals over the age of 65 by 2030. By 2050, the global burden of AD is imagined to augment from 26.6 million cases in 2006 to 106.8 million. Ageing is a natural phenomenon that can lead to cognitive decline in countries all over the world.

Different Hypotheses for Alzheimer' S Disease

Cholinergic hypothesis of AD

Cholinergic synapses can be found all over the human central nervous system. Because of its great concreteness in the thalamus, striatum, limbic system, and neocortex, cholinergic transmission is assumed to be vital in favour of reminiscence, erudition, awareness, and superior brain functions. One of the most outstanding integrant of neuropathology in AD is the loss of cholinergic neurotransmission in the limbic and neocortical regions. Degeneration of Ch4 neurons is more common in AD and loss of Ch4 neurons suggesting that the ultimate aetiology is posterior and anterolateral. In the limbic system, cerebral cortex, and hippocampus, choline acetyltransferase activity is significantly reduced and Memory characteristics are controlled by these areas[9]. In attentional processing, neurotransmission mediated by the chemical acetylcholine (Ach) plays a critical role. Acetylcholine is a neurotransmitter present in the CNS and PNS where Ach is released by the vagus nerve and acts on heart to decrease the frequency of its contractions. It

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affects myoneural junction and autonomic ganglia[10]. Ach is active in the cortex, basal ganglia, and forebrain of the CNS. ACh can imitate numerous brain structures because cholinergic neurons renew existing neurons in presynaptic terminals that produce multiple neurotransmitters. Release of Ach from presynapse can affect glutaminergic activity and GABA neuron activity in the hippocampus. As a result, cholinergic system disruption causes neurotransmitter malfunction, which has a deleterious impact on the brain. Cholinergic neurons liberate Ach which will bind to specific receptor subtypes: nicotinic acetylcholine receptor and muscarinic acetylcholine receptor. Nicotinic Acetylcholine receptors are ionotropic receptors and muscarinic receptors are metabotropic receptors. NAChRs are ion channel receptors with brightly colored pentameric bands composed of mixture of 5 subunits (a, b, c, d and e), all written in the form of distinct genes. The two basic NAChR subtypes revealed in CNS such as a7 and a4b2, which are positively expressed in brain regions that make up AD neuropathology, for this reason affecting those receptors in the pathogenesis of dementia. Due to the presence of a cholinergic wound, nicotinic receptors and muscarinic receptors also cause disease mutations. Reduction in nicotinic receptor binding in AD brain is being tested and in brain region, highly exposed nicotinic α-7 receptors are linked with cognitive processes. A diminish in the number of postsynaptic nicotinic receptors in the cerebral cortex is possible. Only M_2 receptors are reduced in number but M_1 receptors are not reduced in number but their performance is impaired. Thus, a continuous degrade of basal cholinergic neurons in the cerebral cortex elicits the formation of impaired nerves. However, the fact that some parts of the neocortex intercept cholinergic input from the basal forebrain suggests that the ACh location seems to be more vital than attentional function, and numerous studies showed that cholinergic signalling impacts cognition. Cholinergic speculation for vascular dementia stipulates that a scarcity of cholinergic synaptic transmission in intracortical provokes dementia in patients; however, we highlight the role of cholinergic signalling in attentional use, the extent to which mental disorders in AD are a direct result of abnormal cholinergic signalling remains unclear as shown in Figure 1[11].

Another hypothesis for cholinergic dysfunction is insufficiency in neurotrophic hormones. This neurotrophic hormone releases neurotrophins which play an important function in neuronal activity. Nerve growth factor is a class of neurotrophins which is responsible for memory and learning formation. Decrease in the concentration of NGF leads to shrinkage of cholinergic neurons which elicits impaired cholinergic neurotransmission. Neuronal damage and formation of neurofibrillary fractures in the neocortex and hippocampus are hallmarks of AD, which typically paralyse pyramidal neurons and their connections. Neurotransmitters in the medial septum, serotonergic raphe nuclei, and locus coeruleus, which challenge the cortex, are similarly disturbed by neurodegenerative processes[12].

Cholinergic feature out of the doors of nucleus basalis of Meynert, namely, inside thalamus, appears distinctly spared in this system. The underlying mechanism is the place of NBM within the anterior lobe of the forebrain, which consists of limbic system inclusive of the hippocampus, amygdale, and entorhinal cortex. These areas are together prone to neuron deterioration and formation of neurofibrillary tangles. Cholinergic neurons in the medial septum and in NBM are fully depending on retrograde shipping of NGF for conservation of anatomic and biochemical individuality and their fatal synapses cerebral cortex and hippocampus. Synthesis of NGF inside the cerebral cortex is not exaggerated in AD. Animal studies, statistics, and clinical research advocate that the trophic of NGF based cholinergic neurons within NBM can compromise through faulty retrograde delivery of NGF or reduced transformation of pre-NGF to mature NGF, that is neuroguidin. In those with Down syndrome, who're using lofty menace for premature Alzheimer's ailment through means of amyloid β arbitrate mechanisms, elevating plasma degree of amyloid β and inciting scrutinizers are related to biomarker proof of NGF deregulation. NGF deregulation can be triggered by means of accretion of amyloid β and inflammation, the final result is cholinergic loss in NBM.

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Therefore, NGF metabolic pathway stays a capacity pharmacological goal to sluggish degeneration of essential cholinergic function in AD, particularly at preclinical ranges[13]. AD facilitates the participation of pyramidal neurons within the disease as a sample of local hypometabolism resembles neuronal atrophy, production of neurofibrillary tangles, and loss of synapses. Depriving pyramidal neurons in the cortical region, mislaying the synapse, and decreased glutamate awareness, combined with the formation of neurofibrillary connections, are together associated with severity of dementia. These research studies suggest that pyramidal neurons and their transmitter glutamate have an impact on cognitive disorders in Alzheimer's disease[14].

Significance of Amyloid Hypothesis

Amyloid cascade hypothesis asserts that the formation of degeneration of neurons in AD is due to the slow and abnormal accretion of extracellular plates composed mainly of Aβ deposits in various brain regions in the early stages of AD and is ongoing. There is a close relationship between Aβ toxicity, neuronal dysfunction, and decreased memory function[15]. Aβ plaques act as a persistent effect of a cascade containing neuritic plaque, the emergence of neurofibrillary fractures through tau protein effects on the dysfunction of neurons which elicits cell death in AD. Aβ plaques are made up of protein components known as Aβ peptides. Amyloid peptides are 39-43 aminoacid peptides remaining proteolytically formed by enzymatic cleavage of those aminopeptides by β-secretase and γ-secretase in pre-transmembrane amyloid proteins. According to the purification prototype of the APP, the duration of Aβ peptide varies from C-termination. $A\beta_{1-40}$ homolog is the ultimate component and $A\beta_{1-42}$ is naturally hydrophobic and composed of a more hastily than $A\beta_{1-40}$. Inside the plaques, Aβ peptides in the authorized framework combine and disintegrate into formal bureaucrines comprising fibrillar, protofibers and polymorphic oligomers. Formation of Aβ and plaque formation exerts activation of microglial cells, cytokine secretion, active astrocytosis, and an inflammatory response of multiple proteins.

APP is a type I transmembrane glycoprotein revealed in brain and CNS. APP exists in many isoforms fashioned via opportunity splicing. APP gene is positioned on chromosome 21 and those people be afflicted via Down's syndrome with addition duplicate of genetic material broaden, early-onset familial AD. Discovery of the primary precise genetic reason of AD was the incidence of autosomal dominant mutation within APP gene. Several missense mutations were accumulated across the 3 cleavage sites. Swedish mutation in APP gene permits adjustments within amino acid residues at 670 and 671 from Lys-Met to Asp-Leu that will increase Aβ peptide technology through growing β-secretase processing interest While another transmutation modifies the biophysical bustle of Aβ peptide[12].

Amyloids are composed of wreckage of protein molecules. Without looking at temperament of protein, string, amyloid was produced. There are two types of APP processing methods: one is amyloidogenic, and the other is non-amyloidogenic. In non-amyloidogenic pathway, APP is expressed in the form of α secretase that lead to the production of APP (sAPPα). This sAPPα has many protective activities and the AICD has nuclear signature capabilities. In the amyloidogenic pathway, the APP broken down via β-secretase furnishes a covering bound by C-terminal splinter with the intention of attaching to γ secretase and it elicits Aβ peptide. Other enzymes that are able to adhere to APP to location are called BACE 1 and BACE2. It has been depicted with the aim of γ-secretase cut APP next to the border of the cytoplasmic covering and between membranes known as ε-cleavage and γ-cleavage, respectively. In the elderly, decreased metabolic capacity decreases Aβ peptide releasing the deposit of this peptide as shown in Figure 2[16].

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Neuropeptides in Amyloid Cascade Hypothesis

Neuropeptides act as messenger hormones, neurotransmitters, or neuromodulators in CNS. They are very active in memory and behavioural activities. Together with neuropeptides such as corticotrophin-releasing hormone, Angiotensin II, somatostatin and neuropeptide Y contribute to the activation of APP, escalating Aβ and the amyloid cascade hypothesis.

Corticotrophin-Releasing Hormone

Corticotrophin Releasing Hormone is a peptide hormone which contains 41 amino acids and releases corticotrophin. It has an important activity in stress regulation via modulating hypothalamic–pituitary–adrenal axis. CRH acts via CRH-1 and CRH-2 receptors. CRH-1 is found in brain, while CRH-2 splice variation is found throughout the body, with the largest levels of CRH-2 in coronary, heart, and skeletal muscles. It has been discovered that the hippocampus CRH-1 regulates stress-stimulated information acquisition, and that the lateral intermediate septum may also impede learning. Previous research has shown that Cerebro Spinal Fluid (CSF) is produced in brain and have confirmed that CSF CRH is deemed to be subordinate in AD patients compared to sexually transmitted age associated with healthy controls. Increased levels of CRH promote sAPPcy fluid in clonal cells in addition to the number one cerebellar neurons in a CRH-R1 dependent manner. CRH levels can regulate the elevated expression or interest of α-secretase although subduing the exposure or exertion of β-secretase. Cellular mechanical analysis evidences that CRH has a neuroprotective role in AD[17].

Angiotensin II

Angiotensinogen degraded through renin provides Angiotensin I. Next, angiotensin converts ACE to form Angiotensin I to render Angiotensin II. It has a variety of actions on heart, kidneys, vascular gadget, and CNS in physiological and pathophysiological studies. Depending on their discerning relationship, angiotensin receptor subtypes have been identified as AT1 and AT2. Chore of Angiotensin II is included in AD and Angiotensin II violation is associated with improved blood pressure, higher brain infection, and all side effects of AD. Although, it was proven that AT-1 receptor antagonists oppose those methods. Nowadays, administration of Angiotensin II through ICV in Sprague Dawley mice has shown a notable escalate in production of Aβ and β-secretase mRNA and protein range. Aforementioned in vivo research established an important capacity for Angiotensin II in amyloidogenesis by exchanging multiple additives for APP processing method. Therefore, blockade of ACE or AT-1 receptor blockers may be another regulatory objective[18].

Somatostatin

Somatostatin subsists in has two forms, namely, somatostatin-14 and somatostatin-28. These two types present throughout body, especially in the cortex, hypothalamus, brain stem, and spinal cord. Somatostatin behaves in a receptor-mediated style with a G-protein-binding receptor containing five different SSTR1-5 subtypes. It was suggested that somatostatin affects the process of memory and learning. Concentration of somatostatin is deducted in brain and CSF of AD patients. Content of somatotrophin release inhibiting factor has been peculiarly reduced by dementia in the prefrontal cortex of postmortem AD. In addition, deficiency of somatostatin genetics led to hippocampal neprlys in activation, local activation, and elevated levels of Aβ peptide in AD brain. Depending on evidence, increasing the concentration of somatostatin or potentiating somatostatin receptors in brain comes up with the adoption of Aβ peptide by regulating the concentration of neprilysin in AD brain[19].

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Neuropeptide Y

Neuropeptide Y contains a 36 amino acid peptides. NPY is widely expressed in CNS and has many bodily functions. It is believed that they have an impact in conditions of illness that include seizures, chronic pain, and neurodegenerative disorders. NPY levels were found to be low in AD patients. Additionally, a decrease in NPY receptor stiffness was perceived in the temporal cortex and hippocampus in the AD brain. NEP attaches NPYs to C-terminal fragments that secure neuronal cells from the neurotoxic effects of Aβ peptide in humans. Neuroprotective effects of NPY in conjunction with NEP can be used as an alternative treatment for AD. In addition, substance P, galanin, opioid peptides, urocortin, and neurotensin were shown in AD aetiology. Therefore, documented changes in neuropeptides may help to manifest a new healing approaches for AD[20].

Amyloid and Cholinergic Neurotransmission

The incorrect metabolism of APP results in proffering of βA that is a vital phenomenon in familial and sporadic AD. AchE in CNS boom charge of fibril generation via creating a constant multifarious through βA peptides and enzymes are sectarianed by the way of peptides in senile plaques. Coalition of this enzyme with pathological peptides influences the biochemical and pharmacological residence of the enzyme and elevates neurotoxicity of βA fibrils. βA peptides additionally affect ionic homeostasis in cells through means of creating ion channels which may affect cholinergic neurotransmission at a couple of ranges[21]

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Hyperphosphorylation of Tau Proteins

In tau hypothesis, the major causative aspect for AD is tau proteins, which are present within the axons of neurons. Tau is a low molecular weight microtubule scaffolding protein which plays a strong position in assembling and stabilization of microtubules[22]. Human tau gene is localized in chromosome 17. In grown-up human brain, six isoforms of tau protein are enunciated, which might be in particular due to alternative splicing of mRNA with or without exons 2, 3, and 10[23]. Microtubule binding area exists in Exon 10. Insertion of exon 10 offers four-repeat tau isoforms, even as three-repeat tau isoforms are elicited without exon 10. In the adult human mind, each 3R and 4R isoforms are expressed that are allotted in particular in axons of neurons under diseased conditions[24]. In AD patients, hyperphosphorylated 3R and 4R tau proteins are amassed in brain[25]. Tau proteins incorporates diverse amino acids inclusive of arginine, lysine, serine. These aminoacids get changed via the following manner along with phosphorylation, methylation of arginine, acetylation, and monomethylation of lysine and lysine dimethylation[26].

Hyperphosphorylation of tau proteins brings down the affinity of tau towards microtubule stabilization. Assemblage of these pTau in cell bodies without helical filaments known as pretangle. Tau aggregates as twisted fibrils of paired helical filaments called neurofibrillary tangles when they are formed within neuronal cell bodies. However, when NFTs are originated in dendrites or axons are known as threads. This research leads to tau pathology induced by mis-sorting of tau[27]. In stages I and II of AD, tau hyperphosphorylation appears in the trans entorhinal region of brain, which spreads to the limbic region in stage III and stage IV and in stages V and VI it spreads to neocortical areas. Comparing to Aβ accumulation occurring in tau pathology is earlier[28]. Disease producing tau mutations assemble along C- terminal microtubule repeat and the binding capacity of tau with microtubules is reduced and it affects neuronal plasticity. Under pathological conditions, tau proteins are self-aggregated into paired helical filaments and form a fibril seeds and finally hyperphosphorylated in an increased manner[29]. Aggregations of paired helical filaments are stimulated by polyanions. That polyanions interact with tau proteins via positive charge near the ends of tau repeats. Oligomerization of tau proteins interrelated with cognitive dysfunction[30]. Researchers reported that tau oligomers triggered neurotoxic actions that may affect the neuronal skeleton by disturbing the normal interaction patterns[31]. Increased production of procytokines

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such as interleukin-6 stimulates JAK STAT pathway, which accordingly stimulates MAP kinase that increases the activity of transcription factor Erg-1, which escalates the expression of p35. That p35 further activates cdk5 protein kinase enzyme which is involved in neuronal development. Deregulation of cdk5 triggers hyperphosphorylation of tau at Ser 202 and Thr 205, culminating in neuronal degeneration. Thus, degeneration of neurons interrelated with memory impairment. Tau hyperphosphorylation is stimulated by activation of the enzyme kinase p38 as shown in Figure 3[32].

Neuroinflammation Hypothesis

Brain can be a significant wellspring of an assortment of cytokines. Although, endogenously delivered cytokines might impact Aβ aggregation and tangle arrangement in mind, Aβ peptide or tangles could likewise animate microglia, astrocytes, and oligodendrocytes excess production of cytokines and hence create "endless loops" prompting irreversible synaptic misfortune and thus, conduct modifications[33].

Procytokines in Neuroinflammation of Brain

Microglia

Microglia makes up roughly 10% of all cells in the CNS and they are one of the body's first cells to respond to inflammation[34]. Microglia was also discovered in the resting areas, and they were morphologically characterised by sub-soma processes and well-established mechanisms. Microglia in the resting state are able to detect pathogens and ligands generated from the host[35]. Microglia become active in response to invading viruses and adapt morphological changes, such as decreasing their cellular process[36]. In fact, active microglia act a crucial role in a diversity of functions, including activation of cellular debris and degenerative cells in the wound areas, as well as pathogen phagocytosis. In addition, active microglia possess a role in the introduction of antigens to T cells, linking dynamic and reproductive immune interactions throughout the inflammatory response[37]. Inflammatory mediators like cyclooxygenase-2, cytokines, unmixed nitric oxide synthase, radicals such as ROS, and chemicals produced by microglial cells can disrupt the processes of neuronal and cause cell damage.

Astroglia

Astrocytes are subtypes of glial cells within the CNS and they have a considerable participation in the synchronization of neuro inflammation[38]. Astrocytes possess a star-shaped morphology in addition to cellular techniques protracted from the soma[39]. In the healthy CNS, astrocytes are concerned in a couple of physiological procedures, like modulation of oxidative pressure, synaptic transforming, production of growth factors, transmission of neurotransmitters and ion homeostasis[40]. Besides, astrocytes possess extensive participation in the divergence and conservation of dopaminergic neurons. By the cause of interplay through endothelial cells and immediacy to blood vessels, astrocytes participate in the permeability and protection of the BBB, multicellular units engaged in the trade of molecules inside and outside of mind. Astrocytic expression of cytokines and intensification factors regulate the penetrability of BBB in the course of inflammatory conditions and subsequently manipulate penetration of immune cells into the CNS[41]. After pathogenic activation, astrocytes create an extensive compass of inflammatory cytokines. Astrocytes are located with explicit the most important histocompatibility complex magnificence II molecules on their facade, so it acts as an antigen-supplying unit for T cells[42]. On the contrary, liable to their inauguration circumstances and environment, astrocytes can whichever enhances T-cells features. Although, astrocytes main function is neuroprotection, in addition they possess a feature of perpetuating self-destructive surroundings through producing multiple pro inflammatory chemokines, Cytokines and TNF-α. As well, astrocytes physically interact with microglia producing phagocytic capability to exert inflammatory mediators like inducible nitric oxide synthase, IL-12 and TNF-α[43].

Numerous studies have reported that there is a link between neuronal dysfunction and neuroinflammation, linked to stimulation of microglial cells and astrocytes that continue to escalate assembling of proinfigueatory molecules[44]. In AD patients, binding of Aβ enzyme to the underlying cells would produce chronic neuroinfigueation and can lead to improved synthesis of proinfigueatory cytokines such as IL-1β, IL-6, IL-18, TNF-α, TGF-β and progressive tau hyperphosphorylation and neuronal loss. These cytokines are kindred to the etiology of AD. In CNS, astrocyte formation eventually exerts exaggerated oxidative stress and accumulation of proinfigueatory molecules leading to a sequence of neurotoxic processes that cause AD disease. Inflammatory cytokines can act as a biomarker for AD[45].

Interleukin-1

Cytokine IL-1 acts as a mediator of neuroinfigueation in AD by binding IL-1 to a single receptor (IL-1RI) and that receptor interacts with an access protein[46]. The presence of IL-1 around the amyloid plaque leads to plaque formation and excessive depletion of the APP containing FAD mutations[47]. Studies have reported that injecting amyloid beta peptide into the rat brain causes IL-1 production by astrocytes and glial cells[48]. In AD, IL-1 binding increases in microglial cells around amyloid deposition leading to plaque formation. IL-1 is intricate in the origin of amyloid proteins for each *in vitro* and *in vivo* study. Like so, IL-1b promotes APP arrangement in neurons and APP transactions in astrocytes. Moreover, intracerebral injection of IL-1b has brought significant APP stress to the rat brain. These findings suggest that in such a way both microglia and astrocytes respond to the formation of Aβ peptide via secreting IL-1, consecutively, enabling Aβ synthesis, fabricating better commentary expression, thus accelerating Aβ synthesis[49].

Interleukin-6

Interleukin-6 is a multipurpose cytokine which is entangled in the pathophysiology of AD. Binding of IL-6 to a particular receptor activates gp130 homodimerization and JAK STAT pathway which can trigger AD pathology[50]. In AD subjects, increased IL-6 mRNA level in cortex and temporal gyrus of the brain takes place[51]. And, IL-6 promotes APP transcription in cultured neurons. Enhanced synthesis of IL-6 is done by amyloid-beta peptide either directly by astrocytes or indirectly by an IL-1β-dependent process. IL-1 initiates an inflammatory response while IL-6 acts as a secondary cytokine[52].

TNF-α

TNF-α produces neuroinflammation by activating two receptors, namely, TNFRI and TNFRII, and can cause chronic neuroinflammation. When TNFRI gets activated due to the presence of death domain which leads to apoptosis[53]. The major sources for TNFα are microglial cells and astrocytes. TNFα also induces Aβ deposits and triggers the synthesis of nitric oxide. TNFα level is an increased level in patients with neurodegenerative diseases like Huntington's, Alzheimer's disease. However, it was in controversy in TNFα serum and CSF levels. Several evidences are there for an increased level of TNF-α in parenchyma cells of brain. Microglial cells and astrocytes get activated by amyloid beta peptide that results in the production of TNFα [54].

TGF-β

TGF-βs, activins and bone morphogenetic proteins are subunits of TGF-βwhich are present in the CNS. They are named as pleiotropic cytokines, which are participating in the physiological and pathological process of neuroinflammation[55]. TGF-β1 is a unique one of cytokines which binds to a heteromeric complex of serine threonine kinase receptors. This binding interaction elicits neuroinflammation in brain. TGF-β binds to type II receptors and this binding phosphorylates the type I receptor present in the juxtamembrane domain which contains a high concentration of glycine and serine[56]. TGF-β is present in an elevated level in plasma, CSF, intrathecal compartment, and brain parenchyma cells in AD patients. This enhanced TGF-β is

interrelated with cerebral amyloid angiopathy formation. In plaque cells, mainly TGF-β1 is present, but in glial cells TGF-β2 is widely present. Over expression of TGF-β synergizes amyloid deposition in brain of AD patients. Aβ accumulation may be signalled by TGF-β, which can interact with the amyloid beta peptide. Thus, proinflammatory cytokines are correlated with neurodegeneration in AD as shown in Figure 4[57].

Impact of Oxidative Stress in AD

Oxidative stress is a phenomena fall in brain of elderly people and it contributes to a bit part in aetiology of AD. Origination of free radicals, concretely reactive oxygen species from fallacious metabolism of cells or through exposure to radiation and pollutants consequences in accumulation of Aβ peptide and p-tau generation[58]. Escalated oxidative stress occurs in getting older process and outcomes from disproportion between production and cleansing of ROS. ROS products are inevitable, however, undesirable merchandise of physiological functions[59]. These can oxidize important organic molecules like nucleic acids, proteins and lipids. When present in high quantities, it may damage organic system. Brain is peculiarly liable to oxidative strain because it demands exorbitant power, consumes greaterO_2, and presence of multiplied amounts of easily peroxidizable polyunsaturated fatty acids[60]. ROS are produced at some stage in ordinary situations and their quantities are stored low with sensitive stability between the rate of their manufacturing and the rate of their clearance with useful resources of antioxidants and associated enzymes. Thus, the impaired antioxidant systems can surmount the cell redox balance due to oxidative inequality and bring ROS overproduction. ROS are notably reactive, unstable, and have a quick half-life, for this reason creating them challenging to quantify at once. It could be assessed now or not at once through quantifying antioxidant levels or antioxidant enzyme activity[61]. Migration of those species to dendritic spines disturbs the characteristic of receptors present in the synaptic membrane. This physiological process ends in neurodegeneration in major neurons. Oxidation of macromolecules which includes glycated proteins, with increased ROS results inside neurotoxin ceased merchandise and that can induce the discharge of proinflammatory cytokines along with nitric oxide. Metal ions consisting of Cu^{2+}, Zn^{2+} bind to Aβ oligomers and tau proteins catalyse neurotoxic plaques[62]. Thus, oxidative stress, amyloid cascade, and tau hyperphosphorylation are interconnected with each other in AD pathogenesis. Oxidative imbalance and tremendous increase of through-merchandise said in AD.

Lipid Peroxidation

Research studies reported that increased lipid peroxidation occurs in AD. Lipid peroxidation is a phenomenon within which ROS attack lipids and unsaturation present in neuronal lipids via free radical chain reaction producing lipid peroxidation products. These byproducts are aldehydes which are highly reactive, including 4-hydroxynonal, malondialdehyde and acrolein. These byproducts are easily involved in reactions and trigger phosphorylation, improper functioning of tau proteins, and interrupt with the intracellular calcium signalling pathway and it stimulates apoptosis[63]. In AD, 4-hydroxynonal is present in a high level in various regions of brain, which include the hippocampus, entorhinal cortex, amygdala, plasma, and ventricular fluid. Acrolein is found in an elevated level in the cerebellum, middle temporal gyri, and amygdala. Isoprostanes and neuroprostanes are the byproducts of lipid peroxidation, which are found in increased levels in CSF, urine, and plasma of AD patients[64].

Protein Oxidation

Proteins undergo oxidative reactions and react with glycation, glycoxidation, and binding lipid peroxidation products, altogether resulting in ROS production. Biomarkers of protein oxidation are 3-nitrotyrosine and protein carbonyls. 3-nitrotyrosine is produced via condensation of peroxynitrite and tyrosine residues. These compounds are found in elevated levels in brain regions such as hippocampus, frontal cortex, and temporal lobes[65, 66].

Nucleic Acid Oxidation

Nucleic acid contains DNA, RNA, and in DNA, increased oxidative damage occurs in AD patients. Oxidative damage in DNA results in double strand breakage, cross-linking of protein molecules, and modification of base molecules in DNA[67]. In AD, DNA strand breaks are more common in the hippocampal region of brain and in the cerebral cortex. DNA contains adenine, guanine, cytosine, and thymine. Guanine is highly susceptible to oxidation because it has low oxidation potential. Oxidative biomarkers in DNA oxidation are 8-hydroxyguanosine and 8-hydroxydeoxyguanosine, which are byproducts of guanine oxidation[68]. Mostly, RNA is single stranded and cytoplasmic oxidation of RNA was reported in AD patients. This oxidative process leads to accelerated the aging process and chronic diseases like Diabetes Mellitus, cancer, and arthritis[69].

Antioxidants

Antioxidants can greatly increase the viability of neurons in organs. Antioxidants such as vitamin C, vitamin E, and polyphenolics available at reduced the level within brain of AD patients. Moreover, there is a diminution in antioxidant enzyme activity, such as superoxide dismutase, catalase, and glutathione peroxidase[70].

Metal ion redox potential

Copper, zinc, and iron are some of the metal ions which are engaged in neuronal processes[71]. In neurodegenerative diseases such as AD, PD ionic homeostasis has been interrupted and deviates from physiological processes[72]. These metallic ions have the capacity to bind to Aβ peptide, triggering a chain reaction which results in free radical formation[73]. These molecules are stored in the synaptic cleft, where it reacts with zinc to form a neurotoxic plaque. And, these metallic ions react with tau proteins and trigger hyperphosphorylation and form paired helical filaments[74]. Oxidative stress affects both tau phosphorylation and formation of Aβ peptide. Cleavage of proteins by BACE1 is enhanced in the presence of oxidative agents and in hypoxia. ROS production results in excessive formation of Aβ peptide and tau protein oligomers and produces a toxic effects and disrupt neurotransmission[75]. Oxidative stress results in a positive feedback loop which produces enhanced ROS synthesis, Aβ production, and hyperphosphorylation of tau proteins which in turn increases oxidative stress[76].

Mitochondrial dysfunction in Alzheimer's disease

Mitochondria are a cell membrane bound organelle used for ATP synthesis. Mitochondria plays indispensible act in respiratory function and in the synthesis of energy for body. Synthesized energy is essential for biological processes which include the viable capacity of cells. When stimuli are given to mitochondria externally, the structure of mitochondria gets changed as it has metabolic activity of the cell and gets changed due to fission and fusion process. The whole phenomenon is so-called mitochondrial dynamics, which maintains homeostasis[77]. The activity of neurons depends on the energy synthesized by cells and neuronal activity gets disrupted due to mitochondrial dysfunction[78]. Adenosine Triphosphate is a cellular energy formed via mitochondria. Mitochondria are participated in the controlling of secondary messengers including calcium ions and ROS[79]. Mitochondrial dysfunction is characterized by disturbed energy metabolism, accumulation of non-functioning mitochondrial proteins, disfigurement of mitochondrial DNA (augmented level of sporadic mutations in mtDNA). Decreased ATP production occurs as a result of dysfunction of mitochondria. Impairments in mitochondrial electron transport enzymes like Cytochrome Cs oxidase brings about deficient oxidative phosphorylation, altered metal homeostasis, and oxidative stress due to unwanted leakage of electrons during the electron transport chain. Consequently, this brings about overproduction of ROS and so, mitochondrial dysfunction along with oxidative stress acts as a factor in the progression of AD[80].

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Aβ protein accumulation in brain triggered by ROS elicits degradation of the lysosomal membranes and subsequently leads to death of neurons[81]. Phosphatase 2A (PP2A) enzyme is inhibited by ROS. PP2A enhances the activity of Glycogen synthase kinase 3β, which in turn causes tau proteins hyperphosphorylation and forms neurofibrillary lesions[82]. In brains of aged people and AD patients, ROS formation is enhanced as a result of continuous mitochondrial dysfunction. The main target area for oxidative stress is mitochondria[83]. In the etiology of AD, mitochondrial dysfunction occurs as a result of an essential factor of ROS generation[71]. Aβ oligomers are inserted into the double layer of mitochondria which initiates ROS manufacturing, peroxidation of lipids, oxidation of proteins and nucleic acids. Thus, oxidative stress is related to mitochondrial dysfunction as shown in Figure 5[84]. So, strategies such as antioxidants, diet, and regular exercise are needed to deduct ROS levels.

Deficiency of ATP in neurons

ATP is produced by mitochondria via oxidative phosphorylation and this energy is needed for normal cell function. Therefore, mitochondria is known as the Power House of Cells[85]. Electron Transport Chain contains five sequences that occur in the inner lining of mitochondria where the enzyme ATP synthase synthesis ATP, and inorganic phosphate[86]. Mitochondrial malfunctioning in AD is manifested via deduction of brain ATP levels, which is related to the augmented formation of ROS and indicates that mitochondria struggle to organize the electron transport chains. The neurons and glia demand high energy in brain and utilize a good chunk of ATP[87].

Because CNS lacks an energy store, neurons in brain must synthesize ATP in a continuous deal to monitor neurons functioning. Mitochondria is a prime source of cellular energy generation, although aged mitochondria create surplus oxidants, which limit ATP availability and lead to energy loss and excitotoxicity in Alzheimer's disease[88]. Excessive incorporation of ATP synthase subunits is likely to lead to irregular activation of the respiratory chain. Like, ATP-synthase lipid oxidation occurs in the hippocampus and parietal cortex of patients with moderate mental retardation. Combined oxidative phosphorylation contributes to the dysfunction of mitochondria in AD brain, exerting reduced ATP synthesis and oxidative stress which elicits cell death. The legal reduction of ATP synthase exerted through ROS that is a factor in mitochondrial dysfunction in AD, and ROS inhibitory procedures could be purposeful to restore ATP synthase activity[89].

Calcium dysfunction

Calcium is one of the regulators of important neural activities like secretion, motility, body control, synaptic plasticity, proliferation, genetic expression, apoptosis, and mitochondria and have an effective act in cellular calcium homeostasis. There is an augmented production of ROS, blockage of ATP synthesis, activation of cytochrome c mPTP release, stimulation of caspases, and apoptosis when excess calcium is absorbed into mitochondria as such they are overloaded. Internal calcium governs a variety of neuronal activities, and a disruption in this balance can result in neuronal injury and death[90].

Mitochondrial Fission and fusion defects

Mitochondrial fission is primarily mediated via GTPase-related dynamin-related proteins. Protein receptors such as mitochondrial fission factor, mitochondrial fission protein, and mitochondrial dynamics proteins, attract Drp 1 to the OMM. The etiology of several illnesses such as AD and Down syndrome, is characterized by mitochondrial malfunction caused by an imbalance in Drp1 activity. Drp1 is required for the essential activities of mitochondria, including fission, motility, and mitophagy. It is primarily a mitochondrial fission factor that causes mitochondrial fragmentation[91]. Mitofusin-1 and mitofusin-2, dynamin-related GTPases that bind to the outer membranes of the mitochondria are indispensible for outer

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mitochondrial membrane fusion, but optic atrophy type 1 protein encourages inner membrane fusion. Mitochondrial fusion requires the inner mitochondrial membrane's membrane potential to be maintained. Defects in the above enzymes are also required for maintaining the inner mitochondrial membrane's organization and structure. Over expression of tau protein was linked to abnormal mitochondrial fusion. Tau ablation led to a reduction in ROS and an increase in ATP generation. As a result, avoiding tau alterations could improve mitochondrial function[92].

Atypical Mitochondrial transport

Mitochondrial flow ensures that mitochondria are distributed evenly throughout cells. Mitochondrial transport is reliant on proteins found in several mitochondrial compartments, as well as transport molecules and other ion-like compounds found both inside and outside the organelles. The actin cytoskeleton is critical for mitochondrial transport. These mechanisms can ensure normal mitochondrial inheritance and utilisation. ATP delivery to synaptic locations, axonal development, calcium buffering, mitochondrial repair, and degeneration are all critical functions of neuronal mitochondrial transport. Milton proteins, along with kinesin and other motor proteins are responsible for transporting mitochondria. Several human neurodegenerative disorders are linked to impaired mitochondrial axonal transport[93].

Genetic hypothesis

Apolipoprotein E is an amino acid glycoprotein expressed in brain that paves the way for the genetic pathogenesis of AD. There are several isoforms of ApoE specified in brain parenchyma such as apoA1, apoA-II, apoA-IV, apoD, apoE, apoH, apoJ. Particularly, apoA1 and apoJ play a major role in Aβ oligomers. ApoE acts as a binding protein of Aβ plaque and collaborates with it to form neuritic plaques. ApoE alleles have the potential to cause dementia and onset of dementia[94]. In genetic hypothesis, there is an acceleration of amyloid deposits in brain due to an augmentation of cholesterol diet. In addition, cholesterol administration in transgenic APP mice has been found to elevate apoE fabrication in brain and circuitously deduct the concentration of β-amyloid 1-40 and 1-42 in hippocampal region and cortical areas[95]. Reconstituted structures of apo-E lipoprotein complexes successfully shatter extracellular β-amyloid in primary astroglial along with neuronal cell cultures. This event could be simply prevented by utilizing lipoproteins which contains apo B or by a specific LDL-receptor anti-monoclonal antibody[96]. However, the act of apoE in β-amyloid depletion in brain is well renowned in the correct way in which cholesterol directly alters β-amyloid synthesis cannot fully understood[97]. Cholesterol has much roles on the activity of APP secretase. Increased concentration of intracellular cholesterol prevents α-secretase activity but promotes β and γ secretase activity. In cells with high levels of cholesterol esters, β-amyloid generation is notably elevated, and cells devoid of ACAT enzyme thus lowering cholesterol ester levels and increasing intracellular FC, indicating a decrease in β-amyloid production[98].

Presenilins

Presenilins are related to γ-secretase, which is required for the formation of amyloid from a precursor protein. Presenilin genes are overexpressed in neurons as well as neuroglial cells. In CNS illnesses such as hypoxic ischemic encephalopathy or ischemic brain neurodegeneration, excessive presenilin gene loss in lymphocytes may signal indirect neuronal injury. Lymphocytic infiltration was found late after ischemic brain damage for more than a year, according to MRI images[99]. The presence of lymphocytes in the posterior ischemic hippocampus and striatum has been established by immunisation. In addition, postmortem tests revealed lymphocyte infiltration in brains of patients with late-stage ischemic stroke. These findings point to a persistent breakdown of blood-brain barrier in the late stages of cerebral ischemia, which could result in long-term lymphocyte infiltration with overexpressed presenilin genes, which are

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components of secretase over expression.The activation and transcription of effector molecule in these cells during late stages of brain hypoxia-ischemia encephalopathy evinces that they will distract a pivotal contribution in course of disease. These findings may help future studies for a better understanding of the direct function of lymphocyte responses in chronic hypoxia-ischemia[100]. As a result, the balance between degenerative processes and lymphocyte-mediated inflammatory control on neurogenesis can decide long-term impacts of global survival due to hypoxia ischemia, amyloid plaque development, and Alzheimer's dementia.

Infectious etiology

Since AD is a multifunctional disease, microorganisms such as Herpes simplex virus type 1, Chlamydia pneumonia are accompanied with an early stages of AD. HSV 1 virus is the most common virus and has a significant relationship with the pathophysiology of AD due to disruption of blood-brain barrier. Chronic bacterial infection leads to chronic inflammation, exalted amyloidosis affecting regions of brain (hippocampus) that promote neuronal death in brain cells[101]. Several findings suggest that chronic infection with viral, and fungal infections can exert uncontrolled neuroinfigueatory processes, which in turn exacerbate amyloid formation in brain and contribute to AD pathogenesis. Stimulation of microglia commonly seen in the human brain of AD can cause severe neuroinflammation in response to recurrence of HSV 1[102].

Environmental factors for AD

In the modern world, human lifestyle patterns and environmental factors play a minor part in AD risk. Exposure to heavy metals like aluminium, copper, lead, mercury, and insecticides and pesticides in day-to-day life produces neuropathy via neurofibrillary tangles, neurodegeneration in brain regions. Extended exposure of mice to high amounts of Cu resulted in an exalted proportions of brain amyloid protein and neuroinflammation, both of which are considered endorsement of AD progression. Chronic exposure to industrial chemicals and air pollutants contributes a risk for AD[103].

Current treatment strategies

Dementia is caused by a variety of factors, the most pervasive of which is in the elderly is AD. Ongoing memory loss, efficiency, language, and other cognitive skills. Pathological signs include production of amyloid plaques and neurofibrillary tangles in brain, together with neuronal death, synapse squandering, brain atrophy, and inflammation. Although the origin and mechanism of Alzheimer's disease are unknown, two neuropathological symptoms of this disease are extracellular amyloid deposition in the pattern of plaque and intracellular neurofibrillary tangles. Currently available AD medications offer only symptomatic treatment but do not cure disease. Drugs used for AD include cholinesterase inhibitors, NMDA antagonists, antioxidants, a combination of hybrid inhibitors, and synthetic analogues as shown in Figure 6.

Acetylcholinesterase inhibitors

According to the cholinergic hypothesis, loss of cholinergic neurons is the cause of cognitive failure and other symptoms in Alzheimer's disease. AChE inhibitors improve cholinergic neurotransmission via averting Ach from being hydrolyzed and so surging its colligation proportion. Donepezil, galantamine, and rivastigmine have all been demonstrated to be worthwhile in people with mild to severe AD. Although the pharmacokinetics and pharmacodynamics of the three compounds differ slightly, there is no considerablediscrepancy in efficacy. AChE inhibitors are typically tolerated well by patients.

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Tacrine

Tacrine is an Alzheimer's disease medication that is a reversible cholinesterase inhibitor. Tacrine was originally prescribed as a muscle relaxant and a respiratory stimulant. A paucity of acetylcholine, which is attributed to memory loss and cognitive impairment and is caused by the selective death of cholinergic neurons in the cerebral cortex, nucleus basalis, and hippocampus, is an early pathophysiological aspect of AD. Tacrine is hypothesised to have therapeutic effects because of its capacity to improve cholinergic function. This is accomplished by suppressing the hydrolysis of acetylcholinesterase, which raises the concentration of acetylcholine in the cholinergic system. Certain Alzheimer's patients may benefit from tacrine to help them think more clearly. Alzheimer's disease causes numerous chemical alterations in brain. Tacrine will neither cure nor retard course of AD. If this molecular basis is accurate, tacrine's efficacy may fade as the disease advances and fewer cholinergic neurons remain active. However, when Alzheimer's disease develops, the amount of ACh produced decreases, making tacrine ineffective. Tacrine can cause hepatotoxicity. While using this medication, blood tests should be done on a regular basis to see if it affects the liver[104].

Donepezil

Reversible AChE inhibitor, Donepezil binds at the peripheral anionic sites and reduces amyloid plaque accumulation in Alzheimer's patients. Donepezil is used to treat mild to moderate AD, and various scientific research demonstrates that it helps people with severe symptoms of the condition improve their cognitive ability. Patients who received higher dose experience a mild improvement in cognitive capabilities but no change in general performance. On the contrary, a superior pharmacological dosage resulted in a higher prevalence of cholinergic adverse effects in patients, restricting its use. Nevertheless, recent research has suggested that Donepezil can help children with autism improve their speech. Its accessible as a dissolving tablet and an oral solution with 100 percent oral bioavailability, facile BBB bridging, and deliberated elimination. It can be taken once a day since it’s half-life is 70 hours. Drug arrives in doses of 5 and 10 mg, and therapy is typically started with 5 mg for each day and gradually escalated to 10 mg per day after a few weeks. Common adverse effects of Donepezil include nausea, diarrhoea, anorexia, and pain in the abdomen, besides an increase in heart vagal tendency, which causes bradycardia[105].

Rivastigmine

Rivastigmine is a carbamate inhibitor which binds to the esteric portion of the active site and inhibits cholinesterase action. Both BuChE and AChE are inhibited by rivastigmine. It has been approved formanagement of mild-to-moderate Alzheimer's disease in 60 countries, together with all European Union member states and the United States. Medicine is used orally as capsules, syrups, and the 3 mg dose has a decent absorption and bioavailability of 40%. It is excreted in urine and has a low number of drug-drug interactions. Dose started from 1.5 mg twice a day and gradually amplified in an excess of weeks to 6 mg twice a day; the rise is 3 mg for every day for 2 to 4 weeks. Nausea, vomiting, diarrhoea, anorexia, headache, syncope, stomach discomfort, and dizziness are among the side effects that are consistent with the drug's cholinergic effects. Negative effects can be mitigated by utilising a Rivastigmine transdermal patch. Rivastigmine is accustomed to treat Lewy bodies, Parkinson's disease and dementia in addition to Alzheimer's disease[106].

Galantamine

Galantamine is an alkaloid found in the plant Galanthus woronowii that is used for the management of mild to moderate AD. It is a selective, competitive, and retrospective AchE inhibitor that meshes with both anionic and aromatic receptors. Along with, this drug acts as an allosteric ligand on nicotinic cholinergic receptors, altering them. It binds to the nicotinic receptors in binding sites different from those of ACh and

nicotinic agonists, and works to activate the nicotinic receptors in the presence of ACh. Galantamine has a fast and complete absorption rate, with a total oral bioavailability of 80 to 100 percent and a half-life of seven hours. Dose is frequently started at 4 mg twice a day and progressively increases to 12 mg twice a day. The drug has analogous complications as other AChE inhibitors, especially gastrointestinal disorders. Galantamine is less tolerable than other AD medications. Galantamine's allosteric mechanism impacts not merely cholinergic transmission but moreover other neurotransmitter systems such as monoamines, glutamate, and GABA because it has a potentiating outturn on nicotinic receptors. These effects can have a positive effect on mental retardation and mental ill health in schizophrenia, bipolar disorder, and alcoholism[107].

NMDA antagonist

N-methyl D-aspartate is an ionotropic receptor that permits electrical signals to be transferred between brain and spinal column neurons. Electrical signals must travel through NMDA receptors, which must be open. To maintain NMDA receptor, open, glutamate and glycine must bind to it. NMDARs are also found in microglia, and large doses of NMDA cause cortical neurons to die by releasing proinflammatory cytokines. Memantine reduces the extent of amending inward K^+ currents, ensuing microglial cell depolarization, as a direct action on microglial cells. In rodentmodels of AD, memantine is an antimedication that protects neurons from death while simultaneously reducing microglial cell multiplication and activation. Memantine inhibits glutamate's effect on NMDA receptors. It is beneficial in the management of moderate to severe AD as it suppresses extra-synaptic NMDARs, which are activated by excess glutamate. It is well absorbed orally and common adverse effects include dizziness, confusion, headache, constipation, hypertension, and cough. Dosage is normally started at 5 mg and it increases up to10 mg per day[108].

PPAR gamma agonist

Amyloid formation within brain parenchyma is associated with impaired neuronal metabolism and function, eliciting severe neuronal death in AD. Synaptic activity, energy, and lipid metabolism are all affected by this condition. The formation of amyloid plaques triggers an inflammatory response directed at microglia. The ligand-activated transcription factor PPAR gamma is a nuclear receptor that synchronizes glucose the metabolism of lipids while suppressing the inflammatory genes. Thus, agonists of this receptor represent anstrikingsalutaryintention for AD. Benzafibrate, an agonist of PPAR widely used to treat dyslipidemia. Benzafibrate supplementation induces mitochondrial biogenesis, resulting in increased mitochondrial weight loss, increased oxidative phosphorylation, and energy production. Wojtowicz et al., studied PPAR Alpha's New Vision in brain: A Prospective curative Target for Alzheimer's Disease and Other Neurodegenerative Disorders. Xu et al. found that soluble Aβ oligomers unite with synapses and activate signaling pathways downstream, and exerts tau hyperphosphorylation in neurons, oxidative stress, collapse and trouncing of synapses. Mechanisms for the protective effects of Rosiglitazone interfere with the initiation process of Aβ oligomers or through the nuclear receptor signature PPARS or independent PPARS[109].

γ-secretase inhibitors

A 19-transmembrane aspartyl extracellular matrix protease,γ-Secretase is made up of Presenilin, Nicastrin, Aph1, and Pen2. It degrades amyloid precursor proteins to produce Aβ peptide, which encloses a contribution in AD pathogenesis. Reducing configuration of insoluble amyloid-beta is a popular Alzheimer's disease treatment strategy. Breakdown of pre-amyloid protein via gamma-secretase is the concluding step in the creation of ABeta, and GSI has been shown to reduce amyloid load in animal models of AD. Due to its noncompetitive inhibition of γ-secretase, GSI binds to a secretive complexes of an undiscovered allosteric

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compounds. Cleavage activity of the enzyme gamma secretase decreases, which inhibits the synthesis of amyloid beta peptide[110].

Statins

Cholesterol metabolism is linked to numerous risk factors for Alzheimer's disease. Surprisingly, high doses of statins, which are cholesterol biosynthesis inhibitors that prevent mevalonate formation, appear to reduce the progression of AD. Reducing cholesterol synthesis by altering the activity of HMG Co-A reductase through AICAR-mediated AMPK activation leads to a reduction in tau phosphorylation. However, instead of suppressing mevalonate synthesis, this effect appears to be related to AMPK-dependent action of tau. Tong XK et al. showed that in elderly APP mice, simvastatin enhances cerebrovascular function while also lowering soluble amyloid beta levels, inflammation, and oxidative stress. Kurinami et al., carried out the work on fluvastatin prevents amyloid-induced memory impairment in mice, which is linked to a suppression of amyloid build up and oxidative stress[111].

NSAIDs

AD is constituted via inflammatory cells around beta-amyloid peptide deposits and neurofibrillary tangles. Chronic usage of NSAIDs has been proven in epidemiological research, lowering the chance of acquiring AD and delaying the beginning of the illness. Arachidonic acid(AA) is oxidized into eicosanoid lipid mediators such as leukotrienes, thromboxanes, prostaglandins are converted via cyclooxygenase enzymes, are considered effective in inhibiting the activity of COX enzyme. Prostaglandin, COX-2, and AA levels may be high in hippocampus. As a result, fewer NSAIDs are effective like Indomethacin and Ibuprofen combination. Combination of tarenflubril and ibuprofen has the ability to reduce $A\beta_{42}$ synthesis in a COX-independent manner via altering the activity of gamma secretase. According to recent findings, it may work as a neuroprotective agent by reducing neuroinflammation. When Ibuprofen is taken with Cromolyn, plaque development is inhibited[112].

Antioxidants

Pro-oxidant activity of vitamin E

Pro-oxidant agents able to trigger a cascade of oxidative reactions leading to protein unfolding and DNA damages as double-strand breaks. On the contrary, antioxidants at low molecular concentrations contrast the free radicals or convert the radical in an inert compound through oxyreductive reactions. Alpha-Tocopherol is a classical lipophilic antioxidant well known as a scavenger of free radicals in a hydrophobic milieu. However, it can develop both anti- and prooxidant activity in isolated low density lipoprotein (LDL). It is unknown how these activities are balanced in vivo in human plasma.

Vitamin E

Tocopherols and tocotrienols are two types of fat-soluble chemicals found in plants that are referred to as vitamin E. It is an indispensible vitamin for humans, as it helps to keep cell membranes intact. Vitamin E's main function in vivo is an antioxidant, as it is an indispensable lipophilic radical scavenging antioxidant. Because it is the studied form of vitamin E in tissues, α-tocopherol is the most researched. In lipoproteins and cell membranes, α-tocopherol serves as a chain-breaking antioxidant, reducing lipid peroxidation and preserving membrane integrity. Vitamin E has been shown to be able to prevent oxidative damage caused via Aβ in vitro experiments[113]. Gugliandolo et al., demonstrated that vitamin E supplementation may be a useful way to improve cognitive and memory deficiencies via reducing oxidative stress, according to animal models. Furthermore, vitamin E may be more effective when combined with other antioxidants or anti-inflammatory substances. Jahanshahi et al., signified that in rats hippocampi, vitamin E has therapeutic effects on density of congophilic amyloid plaques and neurofibrillary tangles.

Vitamin C

Ascorbic acid is a first-line antioxidant that has various positive effects on the immune system, inflammation, endothelial integrity, and lipoprotein metabolism via redox, oxidative and mitochondrial pathways. Vit-c structure has a lactone ring containing six carbon atoms produced from glucose in the mammalian liver system. Ascorbic acid supplementation appears to reduce cell proliferation, oxidative stress, telomere attrition, chromatin instability, and excessive release of inflammatory markers, as well as increase lifespan. Inflamm-aging and immunosenescence, two markers of biological ageing, were revealed to be positively modulated by ascorbic acid (AA). Ascorbic acid's neuroprotective role is based not only on general free radical trapping, but also on inhibition of proinflammatory genes, reducing neuroinflammation, iron, copper, zinc chelation, and restriction of amyloid-beta peptide fibrillogenesis[114].

Turmeric

Turmeric is generated from curcumin (Curcuma longa - Haldi), which is used in curries and spicy dishes from Asia and Middle East. Curcumin, like many other alternative therapies, has been exploited as a food and then revealed to still have remarkable healing potential. Certain features are considered involved in the degeneration of nerve cells in AD: inflammation, oxidative damage, and, most dramatically, the production of beta-amyloid plaques, along with metal toxicity[115]. Turmeric can penetrate blood-brain barrier and has therapeutic potential by limiting peroxidases, lessening Aβ aggregation, and decreasing neuroinflammation. Turmeric has been designed to reduce the configuration of ROS by engaging neutrophils, inhibiting the activation of proinflammatory cytokines, notably TNF, IL-6, and IL-1. As a result, the critical strategies underlying causing cytokine inflammation are diminished. Turmeric has been shown to directly bind miniscule Aβ species in vitro and in vivo, preventing aggregation and fibril formation[116]. Curcuminoids have been revealed to have persuasive antioxidant properties, as illustrated by own potential to suppress free radical production and propagation. It lowers the oxidation of low-density chylomicrons and free radicals that induce neurodegenerative disorders.

Resveratrol

Resveratrol (3, 5, 4′-trihydroxy-trans-stilbene) is a prevalent phytoalexin in a diversity of crops, particularly grape skin and seeds, that protects against diseases caused by bacteria and fungi. Resveratrol does indeed have bioactivities, including antioxidant, anti-inflammatory, phytoestrogenic, vasorelaxing, cardioprotective, and antitumourogenic properties, all are assisted in the treatment of cardiovascular diseases and cancers, along with degenerative brain disorders besides Alzheimer's disease[117]. Neuronal damage is caused by oxidative stress, which affects intracellular signalling and elicits to neuronal death via necrosis. As a result, in neurodegenerative illnesses, resveratrol is employed to protect against neuronal damage. Several investigations on the antioxidant capabilities of resveratrol have shown that prolonged resveratrol therapy lowered the generation of malondialdehyde and nitrite while also restoring glutathione (GSH) levels. These findings show that this chemical is a viable treatment option for Alzheimer's disease. As a result, resveratrol can control essential glial activities such as uptake of glutamate, GSH, better serviceable resurgence, and suppressed genetic material crumbling and apoptosis, in addition to protecting against ROS[118].

Bioflavonoids -Quercetin

Bioflavonoids are found in the green citrus fruits and in rose hips and black currants. Bioflavonoids have been used in alternative medicine as an antioxidant to enhance the action of vitamin C. Flavonoids have been extensively explored for their antioxidant and anti-inflammatory characteristics, both of which are significant in the aetiology of AD. Flavonoids have been shown to be likely to transmit blood–brain barrier, rendering them potential agents in the mitigation of neurodegenerative disorders. Quercetin is a flavonoid

with remarkable pharmacological properties inclusive of possible medicinal applications. Its dispersed randomly throughout plants, and most of it is found in fruits and vegetables in people's diets. Quercetin is a great source of antioxidants which has been found to substantially diminish superoxide anion free radical concentrations, making it a versatile approach in the treatment of an assortment of illnesses, together with AD. Quercetin has been proven to have direct radical scavenging properties in previous research. Its antioxidant properties are indicative of two pharmacophores in its structure: one is a catechol group, and another is an OH group. Quercetin also affects the cell's own antioxidant pathways by triggering Nrf-2-ARE and the antioxidant enzyme paraoxonase 2 (PON2). Nuclear factor (erythroid-derived 2)-like 2 (Nrf-2) is a foremost regulator of oxidative stress defence in cells. Inhibition of Aβ aggregation and tau phosphorylation are two of quercetin's anti- Alzheimer's disease effects. It restores acetylcholine levels via inhibiting AChE enzyme's hydrolysis of acetylcholine. Although it has been revealed to possess neuroprotective properties in numerous in vitro and animal models [119].

Recent research in Alzheimer's disease

Liu T et al. synthesized4-(1, 2, 4-oxadiazol-5-yl) phenyl)-2-aminoacetamide derivatives and assessed as Alzheimer's disease therapy ligands. 4-(1, 2, 4-oxadiazol-5-yl) phenyl)-2-aminoacetamide derivatives hindered Aβ self-aggregation and decreased BuChE. It also has anti-neuroinflammatory potency in preliminary anti-inflammatory mechanism researches, a representative chemical was revealed to impede the activation of NF- kappa B signalling pathway. It had another DPPH radical scavenging consequence along with an inhibitory effect on the assembly of intracellular ROS. In bidirectional transport assay, this compound exhibited normal blood-brain barrier permeability. Synthesised chemicals augmented memory and cognitive abilities in a mouse model induced by scopolamine[120].

Taqui et al. studied acetylcholinesterase is a serine hydrolase that is required for the hydrolysis of acetylcholine, a neurotransmitter linked to Alzheimer's disease aetiology. Enzymatic inhibition of AChE activity has emerged as a possible Alzheimer's disease treatment strategy. Natural chemicals produced from a variety of plant sources are gaining popularity as possible acetylcholinesterase inhibitors all over the world. The intention of this research was to consider efficacy, usable tissues, model organisms, and extraction data to select species that should be further investigated[121].

Vrabec et al. demonstrated that twenty-two recognised compounds and one undescribed indole alkaloid have been identified from Vinca minor L. (Apocynaceae) aerial portions. A mixture of MS, HRMS, 1D, and 2D NMR techniques were used to determine chemical structures of isolated alkaloids. In vitro acetylcholinesterase and butyryl cholinesterase inhibitory activity of alkaloids extracted in appropriate quantities was tested. Selected substances were lso tested for their ability to inhibit prolyl oligopeptidase and glycogen synthase 3-kinase. (O-2-ethyl-3[2-(3-ethylpiperidinyl)-ethyl]-1H-indole has explored significant BuChE inhibitory efficacy. The manner of inhibition of this drug was investigated further using enzyme kinetics and in silico approaches[122].

Marde et al. studied that sleep disorder is one of the comorbid disorders in people with Alzheimer's disease. Various sleep disturbances, such as Obstructive Sleep Apnea, Excessive Daytime Sleepiness, Rapid Eye Movement, Breathing Disorders, and Periodic Limb Movements in Sleep, are clinical symptoms of sleep disorders. Polysomnography and wrist actigraphy are two of the most common methods for detecting such disruptions. Peter Hauri rules, a sleep education programme, and light therapy are non-pharmacological treatments that help regulate sleep-wake cycles. Pharmacological therapy may be beneficial in the treatment of sleep deprivation in Alzheimer's disease patients. They examined five generally recognised

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plant-based nutraceuticals with theorised impact on sleep problems, including caffeine, chamomile, cherry, L-tryptophan, and valerian, as well as non-pharmacological and pharmacological therapy options[123].

Tumati et al., showed recent blood-based research on agitation in Alzheimer's disease has progressed and search for biomarkers beyond brain, providing fresh insights into the disease's processes and treatment. They discovered that inflammatory biomarkers are elevated in agitated individuals, that they can predict the onset of agitation, and that they are linked to symptom severity. They keep track of symptom intensity along with therapy response. Preliminary evidence suggested that these biomarkers could be used in agitation interventional studies to envisage and scrutinize behaviour response, which could ultimately assist augment research samples and administered therapy that is most liable to assist individuals[124].

Tang et al. focused on the discussion and summary of molecular reasons of Alzheimer's disease. Diverse AD mechanisms depict different molecular and cellular routes in AD pathogenesis, but they are not mutually exclusive. Some AD mechanisms (e.g., amyloid aggregation, microbial infection/neuroinflammation, and amyloid cross-seeding) may also be applicable to other amyloid disorders, including as type II diabetes, Parkinson's disease, and prion disease, from a broader perspective. Such shared processes of Alzheimer's disease and other amyloid illnesses explain not only the pathogenesis of specific amyloid diseases, but also the spread of pathologies between them, inspiring new therapeutic interventions and Preventive strategies for AD[125].

Gowda et al. Discussed mitochondrial miRNAs in regulating mitochondrial ramification; the impact of assorted elements on synapse and mitochondrial function, such as mitochondrial dynamics, biogenesis, Ca^{2+} signalling, natural masculinity, and ageing; how synapse damage and mitochondrial dysfunctions contribute to Alzheimer's disease; organization and utility of synapse and mitochondria in ailment progression; newest investigate buildout in synapse and mitochondria. They explored how changes in mitochondrial miRNA expression impinge on the fabrication of ATP, oxidative stress, mitophagy, bioenergetics, mitochondrial dynamics, synaptic activity, neurotransmission, and synaptotoxicity in AD neurons[126].

Missioui et al., studied that ESI-MS, ^{1}H, IR, and ^{13}C NMR were used to study N-(4-methyl-2-nitrophenyl)-2-(3-methyl-2-oxoquinoxalin-1(2H)-yl) acetamide. Geometric characteristics of NMPOQA compounds, whose crystalline arrangement was determined by means of X-ray diffraction, were computed. Association flanked by experimental and theoretical structures was examined through overlaying the two structures. Frontier Molecular Orbitals were used to calculate the energy gap and intermolecular interactions have also been studied using Molecular Electrostatic Potential and Hirshfeld methods. A fascinating molecular docking study of NMPOQA and Remdesivir with 6M03 was carried out via equivalent specification for a flaxen assessment. NMPOQA is a good contender with COVID-19 because of its low binding affinity compared to remdesivir and other factors[127].

Niikura et al. reviewed humanin (HN) is an endogenous peptide factor that belongs to the mitochondrial peptide family. They discovered the gene encoding this unique 24-residue peptide as an antagonising factor against neuronal cell death caused by AD-related insults in brain of an Alzheimer's disease patient. Their review provided a summary of HN's effects in AD-related circumstances, as well as a brief history of its discovery. HN inhibits a variety of AD-related pathomechanisms, including amyloid plaque production, by acting on both intracellular and extracellular levels[128].

Lichtenthaler et al. discussed secretases are a class of proteases like potential therapeutic targets for AD prevention and treatment. Secretases govern microglial functions by processing both AD-linked neuronal APP and the prompting receptors revealed on myeloid cells. α-secretases, disintegrin, metalloproteases 10 and 17, BACE1 related to AD are highlighted. Novel proteins regulate α- and β-secretase commotion and ultimately, novel potentials as well as obstacles for pharmacologically targeting α- and β-secretase cleavage of APP and TREM2 cleaved through α-secretase with the goal of preventing or treating AD are explored[129]. Barati A et al. researched that in Drosophila models of AD, the independent roles of $A\beta_{42}$ and tau on the inflammatory system, as well as the possible harmonizing consequences of M2000 (D-Mannuronic acid) as a new NSAID. In the treated and untreated groups of M2000, the levels of NF-kappa B, antimicrobial peptide and a dual oxidase like ROS mediator were assessed, followed by brain histological examination to estimate the amount of neurodegeneration. In vitro, the possible inhibitory action of M2000 (D-Mannuronic acid) on tau protein aggregation was also studied. According to their findings, Duox, AMPs, and its transcription factor expression were significantly increased in Drosophila models of AD. Surprisingly, M2000 management resulted in a momentous improvement[130].

Haghighijhoo Z et al. studied quinazolines, a bioactive heterocyclic chemical that has a wide range of characteristics and its scaffold plays an important contribution in the devise and creation of novel CNS medicines. Because AD is a complicated, multifaceted ailment, discovering multitarget medications to combat this debilitating disease is critical. Quinazoline derivatives showed promising modulators of neurotoxic as well as other protective actions in the treatment of Alzheimer's disease[131].

Szabo et al. demonstrated that there was plenty of clinical and biochemical substantiation for endo-lysosomal malfunction in AD, and new inherited research continued to link endo-lysosomal genes to an elevated risk of Alzheimer's disease. Endo-lysosomal network is required in favour of all central nervous system cell types, but each cell type uses cellular trafficking in a distinct way. Challenges ahead include establishing contribution of AD-related genes and perceptive how this exaggerated the cellular malfunction seen in Alzheimer's disease. This is crucial for the development of new therapies that will have an impact on early disease characteristics and maybe reverse them. They evaluated the involvement of certain AD-associated peril genes and reviewed some early evidence of ELN dysfunction in AD aetiology. SORL1, an AD risk gene with variations linked to disease, including APP, through the bloodstream[132].

Yao et al. showed that in 3 Tg-AD mice, α-ketoglutarate dehydrogenase complex, oxoglutarate dehydrogenase-like (OGDHL), was dysregulated. People with AD have lower KGDHC activity in their brains. However, the exact mechanism by which OGDHL played a contribution in enlargement of AD is uncertain. Using RT-PCR, Western blot, and immunohistochemistry, they validated the decreased expression of OGDHL in 3 Tg-AD mice brains. They discovered like upregulating OGDHL can improve memory shortfall, indicating that it has a neuroprotective effect in diseased neurons. In three Tg-AD mice, researchers discovered that increasing OGDHL reduced neuroinflammation, amyloid plaque burden, and phosphorylation of tau. To the basis of Wnt7B expression in vitro, overexpression of OGDHL may triggering wnt/-catenin signalling. Taken together, these findings demonstrate that increasing OGDHL improves cognitive skills through activating Wnt/-catenin signalling pathway. As a result, this enzyme could be used to treat Alzheimer's disease[133].

Ali et al. studied in rat models of aluminium chloride-induced AD, vinpocetine, alone or in combination with EGCG, CoQ10, or VE & Se, has a neuroprotective consequence. Rats were given $AlCl_3$intraperitoneally as a single dose or in combination with EGCG, CoQ10, VE, Se, and vinpocetine for 30 days. Permutation of vinpocetine and EGCG proved to have beneficial in terms of neuroprotection and considerable dwindle in

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Aβ and ACHE in brain showed this protection. The levels of monoamine and BDNF followed the same pattern of results. In addition, when compared to other combinations, vinpocetine and EGCG demonstrated greater anti-inflammatory and antioxidant involvement. These findings were established by means of histopathological examinations. In rats, the combination of vinpocetine and EGCG offered substantial neuroprotection against $AlCl_3$-induced AD[134].

Khalil et al. designed to scrutinize the mutual effects of EGCG and wheatgrass on AD in socialized and isolated conditions. Rats were divided into two groups: socialised and isolated. During the four weeks of the experiment, eight groups of rats were revealed to have psychological and corporeal activities by means of the swimming test and Y-maze. The socialised and isolated groups were both normal, while AD model daily received $AlCl_3$. In addition, they were given saline as a control, EGCG, and wheat grass as treatment. They explored brain behavioural, biochemical parameters and brain portions also subjected to histopathological analysis. Combination of EGCG and wheatgrass provided better mental and physical activities, protection next to the dangers of $AlCl_3$, and isolation than mental and physical activity alone[135]. Wang J et al. discussed the neuroinflammatory mechanisms of AD pathogenesis and H_3R (histamine H_3 receptor) as a presynaptic receptor that synchronizes the release of histamine through negative feedback. H_3R is highly expressed in neurons, microglia, astrocytes and anti-inflammatory properties of H_3R antagonists have been documented. In APP/PS1 Tg mice, they discovered that inhibiting H_3R with thioperamide reduced gliosis and triggered a phenotypic flip in astrocytes, which in turn reduced neuroinflammation. Thioperamide also prevented cyclic AMP phosphorylation response element-binding protein in APP/PS1 Tg mice and decreased phosphorylated P65 nuclear factor kappa B. H89, a CREB signalling inhibitor, reversed thioperamide's suppression of gliosis and proinflammatory cytokine production. Finally, thioperamide reduced amyloid affidavits and cognitive mutilation in APP/PS1 animals, which were both reversed when H89 was given[136].

Chen C et al., studied translational research in Alzheimer's disease was still difficult, emphasising the need for novel AD animal models. They used gavage injections of acrolein to construct a sporadic AD animal models, which revealed typical symptoms after one month. Tau phosphorylation; proliferation of astrocytes and microglia; PSD95 and Synapsin1 decline. High-frequency stimulation botched to produce enduring stimulation in the hippocampus after 4 weeks of acrolein treatment; induce increased T2 signals in the hippocampus and lowered blood oxygen level-dependent symptoms in the olfactory bulb, which matched clinical observations in AD patients and, in the hippocampus of acrolein-treated mice, Rho Aassociated pathway was activated, which could be source of synaptic injury and neuroinflammation in acrolein mouse model. Acrolein-induced sporadic AD mouse model, when combined, resembles the pathogenic hallmarks of AD, making it helpful for studies into the method of AD inception and the progress of anti-AD medicine[137].

Zamanian J et al., focused on Alzheimer's disease dementia, were pathologically linked towards irreversible and progressive protein misfolding, deposition, and accumulation. The pathogenic aetiology of this neurologic dysfunction condition is the production of fibrous amyloid plaques caused by aggregation of amyloid peptides. Furthermore, tau protein isoforms cause neuronal cell death by destabilising microtubule filaments through posttranslational changes. Amyloid-peptide and tau proteins are important symptoms and accurate molecular quantitation for ascertaining AD early on. Because of no effective treatment, expansion of accurate sensing technologies for early assessment is critical. Due to their outstanding sensitivity and specificity, ease of use, cost-effectiveness, mobility, and short assay time, aptamer-based biosensors (aptasensors) have become essential in the field of AD healthcare. They

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highlighted current advancements and fresh ideas in the realm of aptasensor design for quantitative monitoring of Alzheimer's disease biomarkers[138].

Liu et al. demonstrated that laser ablation inductively coupled plasma mass spectrometry has emerged as a prevailing tool for imaging hint components in biological samples. Precisely, quantitative imaging remains a difficult mission owing to a scarcity of matrix-matched reference materials. Traditional LA-ICP-MS analysis, on the other hand, suffers from a long ablation cell washout time and a low laser repetition rate, resulting in slow analytical speed and poor picture resolution. A sequence of handcrafted matrix-matched standards was constructed through homogeneously spiking gelatin with a particular amount of trace elements (Fe, Cu, and Zn). According to quantitative imaging, the allocation and amount of metals differed and the proposed technology is accepted to shed light on metal's biological effects and the origin of metal-related illnesses[139].

Ettcheto et al. showed Dexibuprofen lowers peripheral and central risk factors linked to AD in metabolically challenged APPswe mice. They proved how Dexibuprofen (DXI) affected the progression of Alzheimer's disease in a familial AD model fed a diet of high-fat. Furthermore, during three months, mice were divided into subgroups and given either drinking water or water containing DXI. Body weight, glucose and insulin tolerance tests and behavioural tests were carried out before sacrifice to determine cognitive impairment. In addition, molecular tests were performed in the liver to authenticate metabolic effects to look into a number of pathways known to be hallmarks of Alzheimer's disease. DXI enhanced metabolic alterations in transgenic rats fed an HFD, with outcomes that matched those procured at the molecular level. Improvements in cognitive decline and neuroinflammation were also discovered, as well as other AD-related changes such beta-amyloid plaque deposition and stretched out protein response. Overall, data suggested that taking DXI on a regular basis slows the progression of Alzheimer's disease by reducing inflammation, which helps to improve the pathology's symptoms[140].

Zhao et al. evaluating Ginkgo biloba extract (EGb 761) improves Donepezil's anti-amnestic action via increasing pro-cholinergic and antioxidative properties. It is a standardised leaf extract of Ginkgo biloba L. that has been co-related to favourable effects on neurodegenerative illnesses. The Morris water maze test and ex vivo measurement were used to study pharmacodynamic interactions in scopolamine-induced cognitive mutilation rats treated with vehicle, EGb 761, and Donepezil. Meanwhile, Donepezil and Bilobalide pharmacokinetic profiles was acquired and compared across treatment groups. Despite the positive pharmacodynamic results, two-week co-treatment of EGb 761 and Donepezil had no effect on Donepezil or Bilobalide plasma pharmacokinetics or brain absorption, as confirmed in the hCMEC/D3 monolayer model. In scopolamine-induced cognitive impairment rats, co-administration of EGb 761 and Donepezil produced a greater anti-amnestic effect by enhancing pro-cholinergic and antioxidative actions of EGb 761 or Donepezil without affecting their systemic/brain exposure[141].

Song et al.,carried out Osthole-Loaded Nanoemulsion improved Brain Target in Alzheimer's Disease Treatment through Intranasal Administration. Osthole (OST) is a coumarin molecule found in nature that has a variety of pharmacological actions. The pseudoternary phase diagram approach was employed to create an OST nanoemulsion (OST-NE) in the study.Pharmacokinetic research of OST-NE revealed that the nasal route had a higher brain targeting coefficient than the intravenous method. Furthermore, in L-glutamate-induced SH-SY5Y cells, OST-NE prevented cell death, decreased Bax and caspase-3, and increased the activity of antioxidant enzymes. In Alzheimer's disease model mice, OST-NE enhanced spatial memory skills, raised Ach content, and finally, concluded that employing OST-NE through the nasal route

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enhanced the bioavailability of OST. As a result, OST-NE could be utilised to boost the bioavailability of a drug in the anticipation and management of Alzheimer's disease[142].

Xiang XT et al. studied the build up of amyloid peptides in brain is considered the first sign of AD. Cognitive function has been shown to be harmed by Aβ-mediated neurotoxicity. They wanted to examine O-1602, a selective G-protein coupled receptor 55 agonist, affecting learning and memory impairment in mice generated by intracerebroventricular administration of $A\beta_{1-42}$ (400 pmol/mouse). Injecting aggregated $A\beta_{1-42}$ into brains of mice caused cognitive impairment and neurotoxicity. They also discovered that O-1602 decreased BACE1 activity and soluble $A\beta_{1-42}$ levels in the frontal brain. By encouraging upregulation of PSD-95 and synaptophysin proteins, O-1602 therapy also significantly improved synaptic dysfunction. Furthermore, O-1602 reduced the levels of RhoA and ROCK2, two key proteins intheirpathway, at the same time. By blocking RhoA/ROCK2 pathway, O-1602 was shown to be able to quash $A\beta_{1-42}$induced cognitive mutilation and neurotoxicity in mice[143].

Fakhraei et al. showed AD is a type of brain malfunction marked through progressive memory loss. They wanted to see how aerobic rehabilitation exercise affected the expression of BDNF and TGF-β1 genes in the hippocampal tissue of rats with AD caused by means of amyloid beta injection. Twenty-one male Wistar rats were assigned to three groups: injection, exercise or control. Aβ single dose was injected into rat hippocampus to cause AD. Aβ + exercise group did RhExe for four weeks (5 days/week) starting three days following surgery. After their final training session, the animals were put through Morris water maze test 48 hours later. Mice were euthanized and hippocampal tissue was separated 24 hours after test. BDNF, TGF-β1, and TGF-β1 II receptors' mRNA expression was assessed. Aforementioned was considerably higher in Aβ + exercise group than in Aβ injection group. Aβ + exercise group had significantly higher BDNF gene expression in the hippocampus than Aβ injection group. Aβ + exercise group had considerably better spatial memory than Aβ injection group. Aerobic exercise appears to be able to counteract the negative effects of Aβ via molecular signalling pathways. [144].

Conclusion

Alzheimer's disease is a progressive neurological disorder mostly affecting old age people in developed and developing countries. It is the ultimate cause for dementia and its prevalence is increasing worldwide. Understanding etiology and hypotheses for AD provide an idea for targeted treatment. This review is mainly focused on different hypotheses for AD like cholinergic dysfunction, amyloid plaque, tau protein hyperphosphorylation, neuroinflammation, oxidative stress and mitochondrial dysfunction and its correlation among them and discussed about the availability of current pharmacological treatments. Until now, the only treatment options for AD were symptomatic. Because AD pathogenesis is heterogeneous, it appears that using a multimodal treatment strategy that targets many molecular targets of AD-related degenerative processes is the most realistic way to alter the trajectory of AD progression. Numerous studies have shown that combination therapy is more effective than monotherapy in terms of clinical outcomes. CT is more helpful in the treatment of Alzheimer's disease, especially when started early, as it slows the progression of cognitive impairment. Current Alzheimer's disease treatments, such as cholinesterase inhibitors and NMDA receptor antagonists, provide symptomatic relief but do not prohibit the illness from progressing. As a result, a combination therapy of acetylcholinesterase inhibitors, NSAIDs, antihypertensives, neurotrophic factors, antioxidative factors, and antidiabetic medicines has received a lot of attention recently. Moreover, the emergence of nanomedicines for the treatment of brain illnesses such as AD could inspire a spike in research and clinical availability.

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