A Systematic Review on Alzheimer's Disease

[A dissertation submitted to the Department of Pharmacy, Faculty of Allied Heath and Sciences, Daffodil International University, Dhaka. This report presented in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy.**]**

Submitted To

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APPROVAL

This Project paper, A Review on "**A Systematic Review on Alzheimer's Disease**" submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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Declaration

I, Yeasin Hossain, hereby declare that, this project is done by me under the guidance of Ms. Farjana Islam Aovi, Assistant Professor, Department of Pharmacy, Daffodil International University, in partial fulfilment of the requirements for the degree of Bachelor of Pharmacy. The results embodied in this project have not been submitted to any other university or institute for the award of any degree.

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Certificate

This is to certify that the results of the investigation that are embodied in this thesis works are original and have not been submitted before in substance for any degree or diploma of this university. The entire present work submitted as a thesis work for the partial fulfillment of the degree of Bachelor of Pharmacy.

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-Yeasin Hossain

Dedication

My Parents

The persons who always encourage me in every sphere of my life.

My teacher

The persons who guided me in this process and the committee who kept me on track.

Abstract

Alzheimer's disease (AD), the most common neurodegenerative condition, leads to dementia and cognitive decline. This study's aim is to understand to most prevalent etiology based on Amyloid hypothesis, Tau Hypothesis and microbiological perspective and the Impaired TGF-β1 signalling, systemic inflammation in pathophysiology of Alzheimer's disease. To compare between the diagnostic device with their accuracy, sensitivity and specification. To identify and evaluate all significant randomized controlled trials in order to compare the effects of any pharmacological treatment for Alzheimer's disease patients to placebo. (RCTs). This study has included most of the review paper which has published in PubMed, The Cochrane Library during the year 2013 to April 2023. We included all unconfounded, double-blind, randomized, controlled trials in which treatment with anti-alzheimer's agents were administered to patients with the Alzheimer disease for 24 weeks to 52 weeks. Inclusion criteria: reports with ≥ 50 patients with both sporadic and familial AD. Among 2908 records were retrieved from the systemic database search 57 studies have meet the inclusion criteria (1.96%). The microbiological hypothesis that neurotropic members of the Herpesviridae family influence the neuropathology of AD is now supported by new findings. Impaired TGF-β1 signalling and systemic inflammation can also increasing the risk of AD. In the previous studies already mentioned It is possible to detect abnormalities in the brains of AD patients using a variety of brain imaging techniques, like as PET, MRI, and CT scans, which are thought of as screening tests for illness. But majority studies revealed their accuracy, sensitivity and specification is not satisfactory. In this study briefly analyze the revised diagnosis standards for alzheimer's disease and the use of amyloid biomarkers test mentioned by NIAAA. Several study can't advice 18F-FDG PET, 11C-PIB-PE biomarkers for the routine use. Some studies also found that the MoCA-BC orientation test has strong sensitivity and specificity for identifying MCI, mild AD, and moderate-severe AD. Several studies revealed many major class of drug like cholinesterase inhibitors, tyrosine kinase inhibitor, monoclonal antibodies, aggregation inhibitors, endogenous antioxidant which are beneficial to treat mild to moderate AD. But the most drug has less safe and efficient. But the most recent studies have underlined that the oral hydromethylthionine mesylate has a favourable safety profile. The precise reasons, the method of diagnosis, and the safe and efficient medication for the treatment of AD need to be determined through further research.

Contents

Chapter	Lesson	Topic	Page No.
01		Introduction	01
	1.1	Etiology	03
	1.2	Pathophysiology	04
	1.3	Diagnosis	08
	1.4	Treatment	10
	1.5	Clinical Trials	13
	1.6	Prevention	15
02		Literature review	16
03		Purpose of the Study	19
04		Materials & Method	21
	4.1	Protocol & registration	22
	4.2	Eligibility Criteria	22
	4.3	Information Source & Search design	22
	4.4	Data management & Search strategies	22
	4.5	Data collection process & Data items	22
05		Result	23
	5.1	Therapeutic classes	24
	5.2	Cholinesterase inhibitor	25
	5.3	Tyrosine kinase inhibitor	25
	5.4	Monoclonal antibodies	26
	5.5	Aggregation inhibitor	26
	5.6	Endogenous antioxidant	27
	5.7	Supplementation	27
	5.7	Discussion	28
06		Conclusion	30
07		Reference	32

Chapter One
Introduction

1. Introduction

Globally, there are thought to be 24 million people living with dementia, the majority of whom have Alzheimer's disease. As a result, research into Alzheimer's disease has been designated as a top research priority [1]. More than 15 million people worldwide are affected by Alzheimer's disease, making it exceedingly widespread. Because the disease is heterogeneous and is likely brought on by aging along with a complicated interplay of genetic and environmental risk factors, the origin of the sporadic form of the illness remains unknown [2]. Alzheimer's disease is a chronic condition with 20-year-long preclinical and prodromal phases and an 8–10 year median clinical course. In people over 65, the disease is thought to have a prevalence of 10–30% and an incidence of 1–3%. More than 95% of people with Alzheimer's disease have the sporadic form, which is defined by a late onset (80–90 years of age) and results from the inability to remove the amyloid-(A) peptide from the brain's interstices [3]. Alzheimer's disease accounts for 60% of dementia prevalence in sub-Saharan Africa and India, while vascular dementia accounts for about 30% [4].

According to a meta-analysis, the prevalence of AD in people 60 and older was 1.9% [5]. The cholinergic and amyloid hypotheses were put up as two key causes of AD, and AD is thought to be a complex illness. The condition is also influenced by a number of risk factors, including as advancing age, hereditary factors, head injuries, vascular diseases, infections, and environmental variables [6].

The neurobiology underlying neuropsychiatric symptoms in AD and specific symptoms common to AD as psychosis, agitation, apathy, depression, and sleep difficulties [7]. Trx80 may have potential as a serum AD biomarker because of its association with ApoE4 genotype, age, and many AD risk variables as well as the stage of the illness. Particularly in ApoE4 carriers, increased serum Trx80 and decreased brain Trx80 levels were observed. If this may be a factor in the mechanism that makes ApoE4 more susceptible to developing AD [8]. A strikingly unadulterated memory deterioration is a symptom of Alzheimer's disease. There is growing evidence that this disease starts with subtle changes in hippocampal synaptic efficacy before there is obvious neuronal loss and that the amyloid beta protein, which causes diffusible oligomeric assemblies, is the root cause of synaptic dysfunction [9].

The dominant autosomal mutation in either the presenilin gene on chromosomes 1 and 14 or the amyloid precursor protein (APP) gene on chromosome 21 appears to be the cause of the genetic component of Alzheimer's disease. Moreover, the chance of getting early-onset AD is higher in those with Down syndrome (trisomy 21). Despite the fact that the genetics of AD are more complicated and poorly understood. On chromosome 19, the apolipoprotein E (APOE) gene's epsilon four allele is known to increase the chance of developing sporadic AD [10].

1.1 Etiology

1.1.1 Amyloid hypothesis

According to the amyloid hypothesis, the brain's production of Aß is what causes Alzheimer's disease [11]. The discovery that familial Alzheimer's disease is caused by gene mutations encoding the amyloid-ß precursor protein (APP), with key mutation sites discovered in secretase and APP, provided solid evidence for the amyloid hypothesis [12]. By means of proteolysis in the amyloidogenic pathway, secretase (BACE1) and ß secretase, located in the extracellular and transmembrane regions, respectively, produce Aß from APP. C99 and APPsß are produced during ß-secretase cleavage. Secretase further cleaves C99 to produce either Aß1-40 or the more aggressive, hydrophobic Aß1-42 [13]. Aß40 predominates greater in the cerebral vasculature [14] In the non-amyloid genic route, secretase can also cleave APP, resulting in Appam C83. Further proof emerged from a 1990s study in which transgenic mice expressing three different mutant APP isoforms were discovered to have distinctive neuropathologies of Alzheimer's disease [15]. Despite strong consensus that Aß ibrils are the primary contributor to the pathology seen in AD, it has been proposed that oligomerization of Aß1-42 has a more significant impact. Aß-derived difusible ligands are soluble Aßoligomers that are produced by oligomerizing Aß1-42 (ADDLs).

1.1.2 Tau Hypothesis

The neuroibrillary tangles (NFTs) that are present in Alzheimer's disease are the basis for the Tau hypothesis. Increased phosphorylation of Tau, which was initially attached to microtubules, results in an increase in free tau and a reduction in functional microtubules [16]. PHFs, which make up NFTs, are made up of phosphorylated Tau as one of their constituent parts. Protein transport along axons is impacted by damaged microtubules, which ultimately results in neuronal death [17].

1.1.3 Microbiological perspective

Persistent bacterial, viral, and fungal infections may contribute to AD's inflammatory process. The theory that neurotropic members of the Herpesviridae family, particularly Human herpesvirus 1 (HHV-1), Cytomegalovirus (CMV), and Human herpesvirus 2 (HHV-2), contribute to AD neuropathology is being supported by new research. Several studies have also shown a link between dementia and the Hepatitis C virus (HCV). Spirochetes and periodontal pathogens like Porphyromonas gingivalis and Treponema denticola, which may cause chronic periodontitis and may contribute to the clinical start of AD, are the subject of particular research among microorganisms [18].

1.2 Pathophysiology

Even while dementia is becoming more common everywhere, better vascular treatment and enhanced brain health may have led to a decline in occurrence in the western world. Although amyloid and tau are still required for the diagnosis of Alzheimer's disease, the most common cause of dementia, researchers are slowly moving away from the original amyloid hypothesis's straightforward assumption of linear causality [19]. The molecular pathophysiology of the disease's hallmarks, plaques made of amyloid (A) and tangles made of hyperphosphorylated tau, is now better understood because to developments in science [20]. The primary pathogenic feature of Alzheimer's disease (AD) is the amyloid- formation into amyloid fibrils, which causes a cascade of neurodegeneration [21]. Reduced mRNA expression of APOE, PSEN1, and ABCA7 was seen in AD patients [22]. Amyloid beta (Aβ) aggregation into fibrillar aggregates is a crucial aspect of the pathophysiology of Alzheimer's disease (AD) [23]. Inositol Polyphosphate-5-Phosphatase D (INPP5D) contains the single nucleotide polymorphisms rs35349669 and rs10933431 that are highly linked to the chance of developing Alzheimer's disease [24]. Increased glial senescence, especially localized aggregation of senescent microglia, maintains and propels the progression of AD symptoms, glial aging, and further senescence [25]. According to a study, AD is thought to cause a reduction in adaptive immune function, and the amount of circulating NAbs will probably be used as a biomarker to monitor the disease's progression [26]. The ventral hippocampus CA1's two layers, specifically the astrocytes' ultrastructural characteristics. This location is of particular relevance because prior research using middle-aged and elderly APP-PS1 mice indicated ultrastructural changes as well as increased heterogeneity of microglia, another glial cell type that is severely damaged by AD pathology and is known to be involved in its pathogenesis [27]. In the early stages of cognitive impairment in AD, elevated CSF sPDGFR is related with BBB leakage, which may contribute to cognitive impairment as AD progresses [28].

1.2.1 Impaired TGF-β1 signalling

Transforming growth factor-1 (TGF-1) genetic variants, particularly single nucleotide polymorphisms (SNPs), have also been reported to affect its expression, making TGF-1 a significant risk factor for Late-onset Alzheimer's disease (LOAD). According to studies, TGF-1 can decrease the amount of A plaque deposits in the brain parenchyma, but it can also raise the incidence of A in cerebral blood vessels . In older, healthy people, there is a trend toward higher TGF- levels with age. This is consistent with a similar rise in the prevalence of AD after age 85 and a decrease in TGF-R2 in the brains of AD patients. In order to address the issue produced by decreased TGF-R2 and stop the disease from progressing from mild cognitive impairment (MCI) to full-blown Alzheimer's, a hypothesis has thus arisen through a perspective paper presented by Fessel J. This hypothesis centers on raising TGF- levels. The body of research indicates that TGF-1 signaling is essential for understanding the etiology of AD [29].

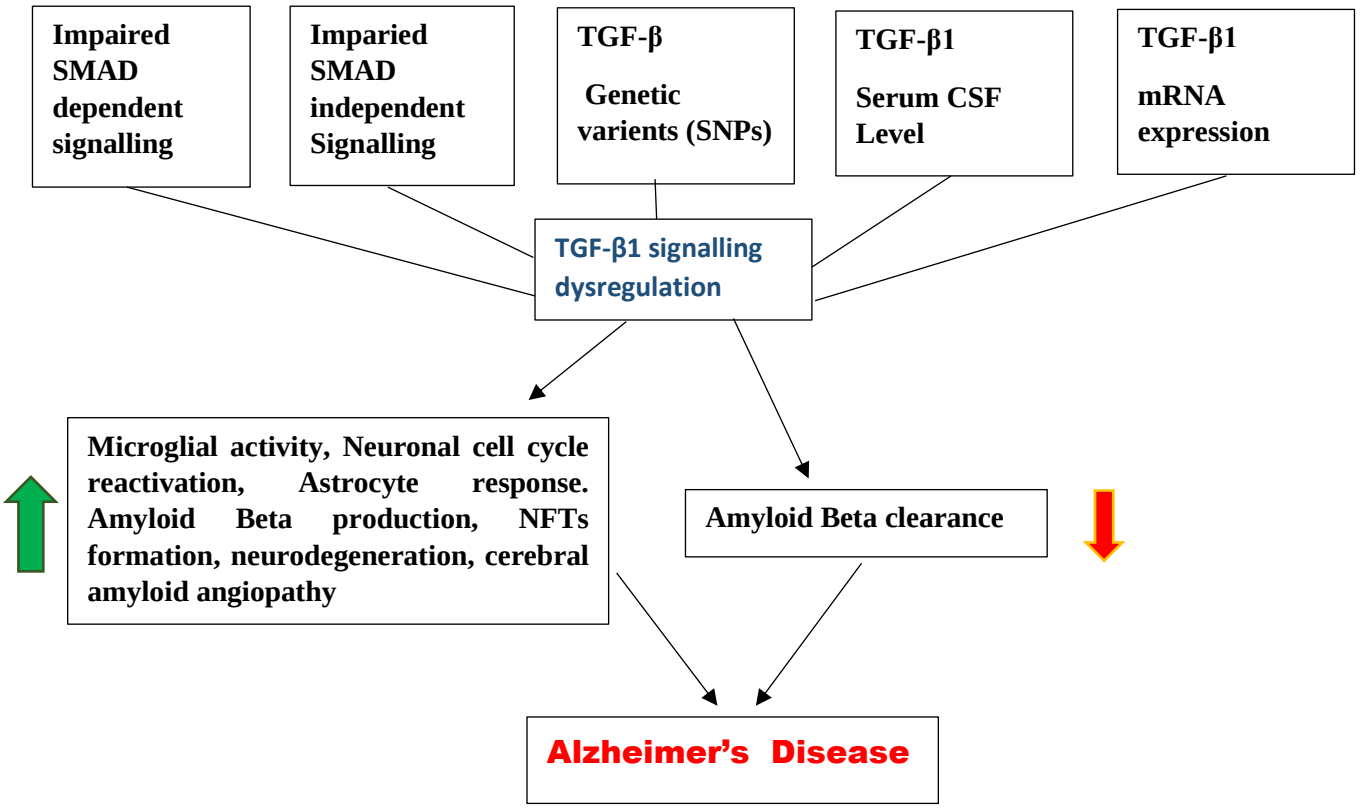

Figure 1.2.1: Impaired TGF-β1 signalling.

1.2.2 Systemic inflammation.

The idea that an infectious agent causes AD directly is not new, but it has largely been based on the idea that there is a particular CNS pathogen that directly affects AD pathogenesis rather than the more general idea that pathogens play a larger role in raising risk by encouraging systemic and central inflammation. As a result, the possibility of the CNS infections Chlamydophila pneumoniae, Borrelia burgdorferi, and Herpes simplex virus type 1 causing the development of AD has been raised. A may be produced in direct reaction to systemic infections and may be a component of the brain's innate immune response to infections, according to some evidence from animal research [30]. It was recently discovered that a second-generation mouse model of AD (AppNL-G-F) likewise exhibits microgliosis and neuronal impairment due to low-grade systemic inflammation brought on by LPS [31]. The body of information, opinions, and theories derived from recent research explains the viral origin as one of the risk factors for the development of AD. The following may be probable modules that happen after infection, which result in long-term damage and brain dysfunction, which finally produce AD pathology, even if the molecular cascade linking systemic inflammation and neuroinflammation is still unknown. To neutralize and remove the pathogen from the peripheral environment, invading microorganisms increase the peripheral A burden [32]. Several studies have revealed a link between systemic infection and neuroinflammation and the initiation and development of AD. According to a review of these research, having an acute or chronic systemic infection during one's lifetime increased

their likelihood of later getting AD [33]. Injections of heat-killed Pg caused systemic inflammation as evidenced by elevated CRP levels in the plasma and gum inflammation as indicated by increased gene expression levels of IL-1 and TNF- in the gums. Increased neuroimmune responses, tau phosphorylation, and systemic immune responses were all seen concurrently. Long-term memory problems were also present in conjunction with these changes. Together, nTg results provide evidence that systemic inflammation brought on by periodontitis contributes to the growth of AD tau pathology, which in turn causes cognitive deterioration. By modifying neuroimmune responses, the direct injection of these two cytokines into the gums of nTg mice may increase the likelihood of AD onset. To sum up, experimental periodontitis-induced systemic inflammation altered neuroimmune reactions, tau phosphorylation, behavior, and cognition, raising the risk of AD [34].

1.2.3 Stem cell line

HEBHMUi013-A

The most prevalent neurodegenerative disease in the world, sporadic Alzheimer's disease (sAD), is characterized by progressive cognitive dysfunction and behavioral impairment. Here, using peripheral blood mononuclear cells (PBMCs) taken from a 78-year-old male patient who had been clinically diagnosed with sAD, we created a human induced pluripotent stem cell (iPSC) line. The iPSC line was able to develop into three germ layers in vitro, exhibited pluripotency markers, and had a healthy karyotype. This iPSC line could be a valuable resource for understanding the pathophysiology of sAD and simulating AD in vitro [35].

IPTi001-A & IPTi002-A

Peripheral blood mononuclear cells from a 62-year-old male patient with sporadic Alzheimer's disease (sAD) and the APOE3 (3/3) genotype were donated (PBMCs). The episomal vector technique was used to create the induced pluripotent stem cell (iPSC) line, which contains the four genes OCT4, SOX2, C-MYC, and KLF4. The ability of the iPSC line to develop into three germ layers was demonstrated by EB differentiation in vitro. NANOG, OCT4, and SSEA4 expression was found in over 90% of cells using flow cytometry. The iPSC line had a normal karyotype as well. The iPSC line might offer fresh, useful resources for researching the pathophysiology of sAD [36].

SPPHIi003-A & SPPHIi004-A

The two induced sAD-hiPSC lines, SPPHIi003-A and SPPHIi004-A, were further developed and verified for their capacity to differentiate into three germ layers in vitro, proper karyotyping, and stem cell-like pluripotency. Notably, both the patient's PBMCs and hiPSCs have the same point mutation on the microtubule associated protein tau (MAPT) gene, which codes for the tau protein and is the crucial

and defining lesion of AD. These recently created sAD-hiPSC lines can be used as a disease model to identify and develop novel treatment targets for sAD and similar hyperphosphorylated Tauopathies [37].

XWHNi001-A

People commonly refer to mutations in the APP gene as the second etiology of familial Alzheimer's disease (AD). Using non-integrative Sendai virus, we created a human induced pluripotent stem cell (iPSC) line from peripheral blood mononuclear cells taken from an AD patient. The iPSC line exhibits the normal karyotype, can develop into the typical teratoma tissue, and highly expresses pluripotency markers. It also retains the APP mutation. The iPSC line will be a helpful tool for researching the pathophysiology of AD and testing potential medications [38].

KEIOi005-A

The KEIOi005-A induced pluripotent stem cell (iPSC) line was created using urine-derived cells (UDCs) from a patient with mild Alzheimer's disease (AD) who also had multiple sAD risk SNPs, including T > C heterozygous APOE 3/4 (rs429358), A > G heterozygous BIN1 (rs744373), and T > G homozygous MS4A6A (rs610932) [39].

PLAFMCi007-A

Peripheral blood mononuclear cells can be used to create induced pluripotent stem cell (iPSC) lines for research into a variety of disorders; in this case, CD34+ cells were extracted from a woman's healthy peripheral blood to create an iPSC line. To create a normal-karyotype iPSC line that expresses distinctive surface markers and other pluripotent stem cell genes and can develop into all three germ layers in vivo, the cells were electrotransfected with three separate recombinant plasmids. These recently developed iPSC lines, which are healthy human cell lines, can be used as a control line in investigations looking into the pathophysiology of different disorders [40].

TOMM40 Genetic Variants

TOMM40 genetic variants are believed to increase the risk of Alzheimer's disease (AD) in different populations. IL-6, IL-18, IL-33, and COX-2 levels in plasma were elevated in TOMM40 missense (F113L) or (F131L) variants. Our findings demonstrate that the Taiwanese population's risk for AD is elevated by TOMM40 exonic variations, particularly rs157581 (F113L) and rs11556505 (F131L). Further research suggests that mutant TOMM40 (F113L) or (F131L) associated with AD causes neurotoxicity of hippocampus neurons by triggering microglia activation, NLRP3 inflammasome activation, and pro-inflammatory cytokine production [41].

1.3 Diagnosis

To make a diagnosis, one must first learn the patient's history. The doctor will find out what symptoms are present, when they started, and how they have changed over time over this time. Furthermore important is the family medical history. A medical examination, including blood and urine tests, will be done by the doctor. This procedure is carried out to rule out additional probable dementia causes, such as hormonal imbalance, vitamin deficiencies, and urinary tract infections. Infections, traumatic brain injury, tumors, and cerebrovascular accidents can all be ruled out with the help of a brain scan. lncRNAs must be viewed as a possible diagnostic biomarker of the disease because they were highly accurate at detecting AD [42]. The distinctive plaques and tangles that are present in AD can be recognized with the use of these images. The volume and shape of the brain are revealed by structural imaging studies like computed tomography (CT) and magnetic resonance imaging (MRI). The doctor can assess the efficiency of brain cell function using functional imaging. It is possible to employ a functional MRI or a positron emission tomography (PET) scan [43].

1.3.1 CT

One of the most affordable neuroimaging methods available is a CT scan. It may create precise images of bone and soft tissue and is a quick, painless process. A number of dangers are there with this approach, though. The patient may experience a dye allergy while being exposed to radiation. The test results could also be interpreted incorrectly and are not applicable to all diseases . CT scans can reliably identify AD while also excluding other potential explanations of the symptoms. Yet, the effectiveness of this kind of scan increases as the disease progresses. The neurofibrillary tangles and beta-amyloid plaques that are present during advanced stages of AD are most frequently identified using this method. Research has demonstrated that MRI and PET scans are more useful for early diagnosis [44].

1.3.2 PET

In Alzheimer disease (AD), which is the most common cause of dementia, the underlying disease pathology most probably precedes the onset of cognitive symptoms by many years. Thus, efforts are underway to find early diagnostic markers as well as disease-modifying treatments for this disorder. PET enables various brain systems to be monitored in living individuals. In patients with AD, PET can be used to investigate changes in cerebral glucose metabolism, various neurotransmitter systems, neuroinflammation, and the protein aggregates that are characteristic of the disease, notably the amyloid deposits [45].

FDG-PET and amyloid PET imaging are useful for evaluating Alzheimer's disease patients [46].The hallmark of AD is glucose metabolic decreases in the parieto-temporal, frontal, and posterior cingulate cortices, according to fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) imaging. Overall, brain metabolic alterations have helped to distinguish AD from other neurodegenerative illnesses and to predict future cases of AD. FDG-PET typically has a sensitivity of 90% for detecting AD, but its specificity for telling AD from other dementias is lower. Furthermore, current MRI-guided FDG-PET investigations have demonstrated that MTL hypometabolism is the most accurate and sensitive indicator of MCI 47]. C-pPIB could serve as a useful biomarker of rCBF for measuring neural activity and improve the diagnostic power of PET for AD in conjunction with 11C-aPIB. 18F-FDG and 11C-PIB dual-tracer PET examination could better detect MCI [48].

1.3.3 MocA

MoCA is a more reliable predictor of cognitive performance since there is no ceiling effect and it can identify cognitive variability better. MoCA demonstrates a higher prevalence of MCI when compared to the MMSE. Both methods identify MCI-related traits that are uniformly modifiable, which is essential information for creating intervention plans [49]. In more than 80% of the studies, MoCA outperformed MMSE at differentiating between people with mild cognitive impairment and those who had none. Both tests were shown to be accurate at spotting AD, with the MoCA screening tool outperforming the MMSE at spotting MCI [50]. Although the MoCA is a promising tool, it has a rather poor level of specificity for detecting early AD [51]. The MoCA-BC orientation test, according to a 2019 study, has good sensitivity and specificity for differentiating between MCI, mild AD, and moderate-severe AD. High sensitivity and specificity were found in the delayed recall memory test for MCI screening. The verbal fluency test was effective at identifying MCI and identifying the degree of AD [52]. These screening technologies' sensitivity fall short of expectations. Nonetheless, given their simplicity in use, these instruments may be useful as a starting point for identifying people who may later need rigorous neuropsychological testing [53].

1.3.4 MRI

Alzheimer's disease progression and disease staging are both considered to be validly determined by MRI-based examination of brain shrinkage (AD) [54]. The primary neuroimaging methods that have demonstrated promise as biomarkers for AD are discussed, with an emphasis on MRI. The most clinically reliable biomarkers for AD currently are structural MRI measurements of the hippocampus and medial temporal lobe, but more recent methods, such as functional MRI and diffusion tensor imaging, offer tremendous potential for tracking changes in the brain, particularly in functional and structural connectivity, which may occur before gray matter atrophy. However, before they are employed as biomarkers to help in the diagnosis of AD, these novel developments in neuroimaging techniques need to be further developed and, more importantly, standardized [55]. The combined use

of MRI and CSF makes a small but significant contribution to the early detection of AD and to tracking its progression [56]. the most recent developments in MRI for displaying the pathogenesis in animal models of amyloidosis. the current difficulties in employing MRI to image the brains of small animals and suggest potential future methods for observing A-related changes in the brains of animal models [57].

7T-MRI

The ability of 7-T MRI to precisely identify iron deposits within active microglia is new evidence that may assist clarify the function of the immune system in the etiology of AD. Finally, the use of 7-T MRI in the identification of microinfarcts shows promise and may help clarify the connection between cerebrovascular health and the course of AD [58].

1.3.5 Gene expression profiling

There is a shortage of reliable diagnostic biomarkers for neurodegenerative disorders (NDDs). For the purpose of detecting Alzheimer's disease, some research produced gene expression profiles (AD). Reduced mRNA expression of APOE, PSEN1, and ABCA7 was seen in AD patients. PSEN1 mRNA expression exhibited promising accuracy for AD, but APOE mRNA expression had good diagnostic accuracy for AD. PICALM mRNA expression performed less well as an AD biomarker. The mRNA expression of ABCA7 and SNCA demonstrated high to exceptional diagnostic specificity for AD. Gene expression analysis offers a liquid biopsy substitute to existing diagnostic techniques and has diagnostic utility for NDDs [59].

1.4 Treatment of AD

1.4.1 Nano-particle to treat AD

The development of nanomaterials for the treatment of AD is based on the promotion of medication delivery across the BBB to achieve accumulation at desirable places. Because of their ability to effectively deliver medications to the target area and boost the therapeutic impact, NPs can carry therapeutic pharmaceuticals by encapsulation or surface modification. Cell membrane biomimetic NPs, which combine NPs with the membrane of the extracted cell, have the major biological characteristics and additional physiological functions of the parent cell. Cell membrane biomimetic NPs used to treat AD are an example of biomimetic nanomedicine, which is still in its inception and has a number of issues that need to be fixed. One of the problems that must be solved before cell membrane biomimetic NPs can be used is preserving their stability, which necessitates a particular stability of medications for long-term effective preservation [60].

1.4.2 Natural Compound to treat AD

Several natural products, including curcumin (Cur), quercetin, thymoquinone, huperzine A, and rhynchophylline , have demonstrated significant promise in the treatment of AD. At the same time, numerous potential natural compounds have been identified from marine algae, including fucosterol, lectin, fucoxanthin, and astaxanthin . In addition to producing a wide range of halogenated chemicals, marine actinomyces are a valuable source of herbal treatments for AD [61]. The -carboline alkaloid harmine and a number of isoquinoline alkaloids appear to be the most promising substances since they can concurrently block a number of important enzymes involved in AD's pathogenesis [62]. Natural products in general possess numerous advantageous qualities for drug discovery and development, including being anti-inflammatory, diversely bioactive, less toxic, readily available, and adaptable natural compounds with the ability to prevent and treat AD symptoms [63]. No stable evidence found specifically workd on AD but work on nueroinflammatorty disease. And symptomatic reduction.

1.4. 3 Acetylcholinesterase inhibitor

Cholinesterase (ChE) inhibitors, which have been authorized to treat the signs of Alzheimer's disease, have been preventing acetylcholine hydrolysis for more than ten years (AD).

Cholinesterase inhibitors (CI) strive to increase the availability of acetylcholine in synaptic neurotransmission to solve memory issues [64]. Tacrine-propargylamine compounds were created and investigated for their potential to treat Alzheimer's disease (AD). Compounds 3a and 3b among these derivatives had superior activities and a favorable balance of AChE and BuChE activities. Moreover, compounds 3a and 3b showed negligible neurotoxicity and roughly 5- and 28-fold higher hAChE inhibitory efficacy relative to tacrine. These substances were also less hepatotoxic than tacrine, which is significant. Potential lead drugs for the treatment of AD include compounds 3a and 3b [65]. Patients with mild to moderate AD can effectively treat their neuropsychiatric symptoms with donepezil [66]. Donepezil, galantamine, rivastigmine, and memantine are the four most often utilized medications. Acetylcholinesterase inhibitors with various pharmacologic and pharmacokinetic features include donepezil, galantamine, and rivastigmine. The acetylcholinesterase is specifically inhibited by donepezil, which also has a lengthy elimination half-life (t(1/2)) of 70 hours. Galantamine affects presynaptic nicotinic receptors in addition to being a selective acetylcholinesterase inhibitor. It has a half-life of 6–8 h. Cytochrome P450 (CYP) 2D6 and CYP3A4 in the liver are primarily responsible for the metabolism of donepezil and galantamine. Acetylcholinesterase and butyrylcholinesterase are supposedly "pseudo-irreversible" enzymes that are inhibited by rivastigmine. The drug has a very short half-life (1-2 h), but because it blocks the enzymes for 8.5 and 3.5 hours, respectively, it has a longer duration of action [67]. Side effects as a result of Cholinesterase Inhibitors are minimal and are usually limited to gastrointestinal symptoms such as diarrhea, nausea and vomiting.

1.4.4 NMDA Receptor Antagonists

Memantine, a partial N-methyl-D-aspartate receptor (NMDAR) antagonist, is marketed in the United States and Europe as Namenda (Forest), Axura and Akatinol (Merz), and Ebixa and Abixa (Lundbeck) for the treatment of moderate to severe Alzheimer's disease (AD) [68]. Several ligand-gated ion channels can interact with memantine. However at therapeutic dosages, memantine seems to have NMDA receptors as a primary target. A non-competitive (channel-blocking) NMDA receptor antagonist is memantine. Memantine can disrupt synaptic plasticity mechanisms that are thought to be responsible for learning and memory, just like other NMDA receptor antagonists when used in high quantities. Yet, memantine has the potential to stimulate synaptic plasticity, retain, or improve memory in animal models of AD when used at lower, clinically relevant dosages [69]. Memanine is recommended by the NICE guidance from 2011 for use in the NHS's treatment of people with advanced Alzheimer's disease. For those with intermediate Alzheimer's disease who are unable to take cholinesterase inhibitor medications due to adverse effects, NICE also suggests memanine.

1.4.5 Psychotropic drug

SRIs

SRIs have anti-inflammatory properties that may help treat Alzheimer's disease and other neurodegenerative diseases. Fluvoxamine and fluoxetine, for instance, seem to suppress the NLRP3 inflammasome, an immunomodulatory function that might be used to treat macular degeneration and other diseases with neuroinflammation or peripheral inflammation as their underlying pathophysiology. In addition to these anti-inflammatory actions, trazodone, vortioxetine, and fluvoxamine appear to have neuroprotective benefits in the context of CNS amyloid deposition (a precursor to Alzheimer's disease). Due to their sigma-1 receptor agonist action, many could be helpful in neuropsychiatric illnesses. Finally, SRIs appear to decrease amyloid formation and aggregation60; they may work well in conjunction with drugs that accelerate the clearance of amyloid plaques [70].

Atypical antipsychotic drug

The majority of investigations have shown the atypical antipsychotics to be effective. Moreover, antipsychotic drugs including risperidone, aripiprazole, olanzapine, quetiapine, and pimavanserin have a good tolerability rate in the treatment of AD [71].

The Role of ATF family in treatment of AD

ATFs may play a role in the development and management of AD, claims a study. Given that AD drastically alters the expression of ATFs, it is possible that ATFs are the gene responsible for AD. As a result, it is possible that AD therapies could target ATFs. Various ATF kinds play various roles during AD. Via a variety of mechanisms, including the control of apoptosis, neuroinflammation, oxidative stress, and ERS, they may contribute to AD. As a result, targeting ATFs for the treatment of AD may be beneficial. ATF4, also known as CREB-2, is a transcription factor that is a member of the ATF/CREB family and has been shown to be crucial in the mouse model for synaptic plasticity, memory suppression, and memory enhancement. ATF4 is a possible target for treating AD as it can prevent Aβ1-42-induced neurodegeneration when the ATF4 gene is silenced by siRNA alone in axons [72].

1.5 Clinical Trial

1.5.1 Aducanumab

A monoclonal antibody called Aducanumab is specific for amyloid (A) aggregates. Acurenumab was the first medication under the accelerated approval pathway to be approved by the US Food and Drug Administration (FDA) and address the pathophysiology of Alzheimer's disease (AD) in June 2021. A combination therapeutic approach for AD (anti-tau and anti-amyloid medication) may be possible as a result of the aducanumab's demonstration of an impact on downstream tau pathology. The Peripheral and Central Nervous System (PCNS) Medicines Advisory Committee convened on November 6, 2020, to discuss aducanumab's clinical data. The members did not approve aducanumab by a single vote (10 against, 1abstention). They believed that the study findings were contradictory and that the data did not sufficiently demonstrate therapeutic efficacy [73]. Auranumab's effectiveness is debatable, and there are also worries about its side effects. Acuranumab has primarily been associated with amyloid-related imaging abnormalities (ARIA), which include edema and microhemorrhages. ARIA was formed by 41.3% of trial participants who got higher-dose aducanumab therapy. About 25% of those with ARIA experienced associated symptoms, such as headaches, disorientation, dizziness, and nausea [74].

1.5.2 Lecanemab

Lecanemab, a humanized IgG1 monoclonal antibody that fights soluble aggregated A species (protofibrils), has effectively reduced brain fibrillar amyloid and slowed the progression of early-onset Alzheimer's disease. Amyloid plaques were significantly reduced after receiving lecanemab therapy, and the rate of clinical decline was also slowed. The possibility of using plasma biomarkers to track the effects of lecanemab treatment is suggested by the data, which also show that rapid and dramatic amyloid reduction correlates with clinical benefit and possible disease-modifying effects [75].

1.5.3 Hydromethylthionine mesylate

In two completed Phase 3 trials in mild/moderate Alzheimer's disease, hydromethylthionine mesylate, a tau aggregation inhibitor, was demonstrated to exhibit exposure-dependent pharmacological effect on cognitive decline and brain shrinkage (AD). The data will offer additional support for hydromethylthionine mesylate's clinical and biomarker advantages in mild to moderate AD. Low-dose oral hydromethylthionine mesylate would probably enhance AD care because it is straightforward to use therapeutically, does not result in amyloid-related imaging abnormalities, and has a benign safety profile [76].

1.5.4 Masitinib

Study **AB09004** is the first effective tyrosine kinase inhibitor targeting innate immunity cells in a controlled, randomised, phase 3 experiment in AD. These encouraging clinical results suggest that mast cells and/or macrophage/microglia are involved in the pathophysiology of mild-to-moderate AD, possibly by changing the neuro-immune system from a neurotoxic state to a neu-roprotective state through remodeling of the neuronal microenvironment. This is consistent with the known targets of masitinib [77].

1.5.5 Donepezil

This was a phase III, 24-week, multicenter, double-blind, double-dummy, parallel group, non-inferiority trial that was conducted in Japan. 303 of the 340 randomly assigned patients finished the double-blind phase. The Japanese version of the Alzheimer's Disease Assessment Scale's cognitive component showed changes from baseline at week 24 of -0.7 + 0.4 (donepezil patch 27.5 mg) and 0.2 + 0.4 (least squares mean standard error) (donepezil hydrochloride tablet 5 mg). The 95% confidence interval for the difference in the least squares means was -0.9. (-2.01 to 0.14). In Japanese individuals with mild-to-moderate Alzheimer's disease, non-inferiority on the suppression of cognitive deterioration was demonstrated for the donepezil patch 27.5 mg when compared to donepezil hydrochloride tablets 5 mg [78].

1.5.5 Endogenous antioxidants

For people with Alzheimer's disease (AD), sodium benzoate may have the ability to improve their cognitive function, according to earlier pilot research. A confirmatory experiment using prognostic biomarkers is urgently required, particularly for AD therapy. Three large Taiwanese hospitals carried out a 24-week, dose-finding, randomized, double-blind, placebo-controlled experiment with clinical assessments at weeks 0, 8, 16, and 24. With higher baseline catalase predicting better response, sodium benzoate therapy enhanced cognition in AD patients by boosting two essential endogenous antioxidants, catalase and glutathione. The findings support the oxidative stress theory and point to benzoate as a potential new AD treatment [79].

1.5.6 Rivastigmine

3450 patients' worth of data from seven trials were included in this research. Due to a lack of data and methodological issues, two additional studies' data were excluded. All of the included trials had a mean age of roughly 75 years and enrolled people with mild to moderate Alzheimer's disease. The risk of bias due to attrition was uncertain in four research, low in one study, and high in two studies, although all showed low risk of bias for randomization and allocation. Rivastigmine appears to be helpful for persons with mild to moderate Alzheimer's disease (6–12 mg daily or 9.5 mg daily transdermally). Better results were seen in compared to placebo for the rate of deterioration in cognitive function and activities of daily living, even if the effects were minimal and of questionable clinical significance. Additionally, rivastigmine had a positive effect on the results of the clinician's overall assessment [80].

1.6 Prevention

1.6.1 cysteine protease inhibitor

The success or failure of preventative trials may depend on the accuracy of the clinical event assessment [81]. The accumulation of amyloid peptides (A) in the brain, which have a potential neurotoxic effect, is thought to be a primary contributing factor to the onset of Alzheimer's disease (AD). Hence, it appears that preventing amyloid polypeptide aggregation is a viable strategy for treating and preventing this neurodegenerative disease. Ovocystatin, a cysteine protease inhibitor purified from egg white, inhibits the in vitro formation of A-42 fibrils. Ovocystatin's ability to suppress the production of amyloid fibrils has been evaluated using thioflavin-T (ThT) assays, which detect the amount of amyloid peptide aggregation based on fluorescence measurements, circular dichroism spectroscopy (CD), and transmission electron microscopy (TEM). The MTT test was used to gauge the toxicity of amyloid beta 42 oligomers. According to the findings, ovocystatin suppresses A42 oligomer toxicity in PC12 cells and has anti-A42 aggregation activity. The findings of this research could aid in the creation of possible drugs that could stop or slow the beta-amyloid aggregation process, which is one of the main causes of Alzheimer's disease [82].

1.6.1 Supplementary

In a double-blind, placebo-controlled, randomized clinical trial, patients with mild-moderate AD received daily doses of 1 g fish oil (of which 500 mg DHA and 150 mg EPA), 22 mg carotenoids (10 mg lutein, 10 mg meso-zeaxanthin, and 2 mg zeaxanthin), and 15 mg vitamin E, or a placebo, for 12 months. Interventions that help to reduce symptoms and enhance quality of life in AD patients are required due to the exponential rise in AD prevalence and the disease's unrelenting progression. Given the successful results of this experiment, AD therapy should take this combination micronutrient dietary supplement into account [83].

Chapter Two

Literature Rivew

2.1 Title:

Alzheimer's disease: Recent treatment strategies

Authors: Vaz M, Silvestre S. Alzheimer's disease: Recent treatment strategies. Eur J Pharmacol. 2020 Nov 15;887:173554. doi: 10.1016/j.ejphar.2020.173554. Epub 2020 Sep 15. PMID: 32941929.

Two neuropathological hallmarks of Alzheimer illness (AD), a neurodegenerative illness, include intracellular neurofibrillary tangles and extracellular amyloid plaque formation. Donepezil, galantamine, rivastigmine, and memantine are the only treatments now available for AD, and they only provide symptomatic relief. Consequently, it has been a top focus to discover medications that may alter how the disease develops. For almost 30 years, amyloid-targeting therapies have been the main focus. However, recently, phase III trials for highly anticipated medications failed to demonstrate clinical advantages. Even the promising results Biogen reported for Aducanumab are not conclusive, and more evidence is required to support them. Since tau protein seems to be more correlated with the degree of cognitive loss than amyloid, researchers are now focusing their attention on tau-targeting medicines. The majority of anti-tau medications currently undergoing clinical trials are immunotherapies, and these studies are still in their early stages. To date, phase II has been reached for four anti-tau monoclonal antibodies (Gosuranemab, Tilavonemab, Semorinemab, and Zagotenemab) and one anti-tau vaccination (AADvac1). We explore prospective disease-modifying pharmaceuticals tested in clinical trials and provide updated data on medications now undergoing clinical evaluation in this study.

2.2 Title:

New Pathways Identify Novel Drug Targets for the Prevention and Treatment of Alzheimer's Disease

Authors: Penke B, Szűcs M, Bogár F. New Pathways Identify Novel Drug Targets for the Prevention and Treatment of Alzheimer's Disease. Int J Mol Sci. 2023 Mar 11;24(6):5383. doi: 10.3390/ijms24065383. PMID: 36982456; PMCID: PMC10049476.

Alzheimer's disease (AD) is a neurological ailment that is progressive and incurable. 60–80% of dementia cases are caused by AD, a complicated and multifaceted illness. The main risk factors for AD are aging, genetic predispositions, and epigenetic modifications. Amyloid (A) and hyperphosphorylated tau are two aggregation-prone proteins that are crucial to the development of AD. (pTau). In the brain, they both cause deposits and toxic aggregates that can spread. The AD biomarkers are these proteins. To understand AD pathophysiology and provide a foundation for AD medication research, various hypotheses have been put forth. Studies showed that both A and pTau are required for cognitive impairment and may initiate neurodegenerative processes. The two diseases work together. The

prevention of the synthesis of harmful A and pTau aggregates has long been a therapeutic target. Recent developments in the treatment of Alzheimer's disease (AD) if it is discovered in its early stages have given rise to new optimism. Recent advancements in amyloid clearance from the brain, the use of small heat shock proteins (Hsps), the modulation of chronic neuroinflammation by various receptor ligands, the modulation of microglial phagocytosis, and an increase in myelination are just a few examples of novel targets that have been identified in AD research.

2.3 Title:

Potential mechanisms between periodontitis and Alzheimer's disease: a scoping review

Authors : Lamphere AK, Nieto VK, Kiser JR, Haddlesey CB. Potential mechanisms between periodontitis and Alzheimer's disease: a scoping review. Can J Dent Hyg. 2023 Feb 1;57(1):52-60. PMID: 36968797; PMCID: PMC10032644.

The direct transfer of periodontal germs from the oral cavity to another organ system and inflammation brought on by metastatic periodontal inflammation have both been proposed as potential ways by which the periodontal inflammatory response may communicate to distant organs. Examining these processes as a possible connection among periodontitis and Alzheimer's disease is the goal of this scoping review. Using keywords or keyword combinations like Alzheimer's disease AND periodontitis OR periodontal disease AND inflammation, a reiterative literature search of peer-reviewed articles was carried out in the PubMed and Scopus databases. There were 777 articles found in all. 84 papers were chosen for full-text review after duplicates were removed and after titles and abstracts were reviewed. 19 publications that were eligible for the study after full-text review. The literature review demonstrates how periodontitis may cause neuroinflammation by introducing periodontal bacteria and/or locally generated proinflammatory cytokines at the periodontium. Both the development and progression of periodontitis and Alzheimer's disease have a crucial role for inflammation. However, further research is required to fully comprehend the complex pathophysiology of Alzheimer's disease.

Chapter Three

Purpose of the study

3. Purpose of the study

- To provide the most promising directions of finding the clues for preventing and delaying the development of AD.
- To identify prospective biomarkers and quantify their effect on AD progression.
- To understand to most prevalent etiology based on Amyloid hypothesis Tau Hypothesis and microbiological perspective.
- To understand the Impaired TGF-β1 signalling, systemic inflammation in pathophysiology of Alzheimer's disease.
- To identify the helpful tool for researching the pathophysiology of AD and testing potential medications
- To compare between the diagnostic device with their accuracy, sensitivity and specification.
- To analyze the studies on the treatment of AD, also considering mild cognitive impairment (MCI).
- To assess study factors that impact the association of cognitive disorders in people with AD.
- To summarize evidence on drug interventions in MCI and mild AD.
- To identify and evaluate all significant randomized controlled trials in order to compare the effects of any pharmacological treatment for Alzheimer's disease patients to placebo. (RCTs).
- To find out the possible prevention strategy of AD from most recent clinical trials.

Chapter Four

Materials & Method

4.1 Protocol and Registration

This Systematic Review has adhered to the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines.

4.2 Eligibility criteria

In order to assess the etiology, pathophysiology, diagnosis, prevention and treatment of Alzheimer's disease. We included all original studies, evidence, mechanism, diagnosis process (sensitivity. Specificity, accuracy), clinical trials of AD. This study include the human studies and exclude the non-peer-reviewed studies written in English language.

4.3 Information source and search strategies

By using relative keyword, a systematic review done in Cochrane library database, Pubmed and Google scholar. In order to conduct a systematic search, this study used the following search keywords in selected databases ("Alzheimer Disease/diagnosis"[Mesh] OR "Alzheimer Disease/drug therapy"[Mesh] OR "Alzheimer Disease/epidemiology"[Mesh] OR "Alzheimer Disease/etiology"[Mesh] OR "Alzheimer Disease/physiopathology"[Mesh] OR "Alzheimer Disease/therapy"[Mesh]).

4.4 Data management & Selection process

In total, we used the findings of our extensive search to import 2,908 articles into Endnote X20. After removing the duplicates, this study looked through papers based on their titles and abstracts to discover every study that met the criteria. The entire texts of the included studies were purchased and objectively reviewed in compliance with the inclusion and exclusion criteria. The likelihood of differences across data extraction files was evaluated, and any disagreements were resolved by consensus.

4.5 Data collection process & Data items

From each included study, This study extracted following information, including title, tome of publications, Publisher's name, number of all included participants. We included all unconfounded, double-blind, randomized, controlled trials in which treatment with anti-alzheimer's agents were administered to patients with the Alzheimer disease for 24 weeks to 52 weeks.

Chapter Five

Result & Discussion

5. Result

2908 records were retrieved from the systemic database search. 321 duplicate records were removed and 627 records have been removed for other reasons by Endnote Software, and 321 reports were sought for screened. Only 289 reports have assessed the eligibility criteria. Finally, a total of 57 studies have been included in the review.

5.1 Different Therapeutics classes of medication used in the treatment of Alzheimer's disease

Therapeutic class	Name of the drug	Mechanism of action
Cholinesterase inhibitor	Donepezil Rivastigmine Mastinib	Prevents the breakdown of acetylcholine and butyrylcholine in the brain
Monoclonal antibodies	Aducanumab Lecabemab	Selectively binding amyloid aggregates in both the oligomeric and fibrillar states
NMDA receptors antagonist	Memantine	Inhibiting glutamatergic neurons via extra-synaptic NMDA receptors
Aggregation inhibitor	Hydromethylthionine mesylate	Breakdown the tau aggregation.
Tyrosine kinase inhitor	Mastinib	Selectively inhibit the phenylaminothiazole-type tyrosine kinase
Endogenous antioxidants	Sodium benzoate	Decreased GSH levels and increased MDA levels in the brain.

Figure 5.1: Therapeutic classes

5.2 Cholinesterase inhibitor

Donepezil

The review's inclusion criteria were met by 30 research with 8257 participants, 28 of which provided results in enough depth for the meta-analyses. The majority of trials lasted six months or fewer. One brief trial only lasted 52 weeks. In the research, donepezil capsules at doses of 5 or 10 mg/day were mostly evaluated. A slow-release oral formulation that provided 23 mg per day was tried in two experiments. 21 studies involved participants with mild to moderate disease, five studies with moderate to severe disease, and four studies with severe disease. There is moderate-quality evidence that donepezil treatment for durations of 12 or 24 weeks results in modest improvements in cognitive performance, daily living activities, and clinician-rated global clinical state in patients with mild, moderate, or severe dementia caused by Alzheimer's disease.

Rivastigmine

13 trials in total fulfilled the review's inclusion requirements. The studies lasted anywhere from 12 to 52 weeks. In earlier studies, a capsule form with a daily dosage of up to 12 mg was examined. Continuous dosage transdermal patch formulations giving 4.6, 9.5, and 17.7 mg/day have been investigated in studies reported since 2007. 3450 patients' data from seven trials were included in this research. Rivastigmine appears to be helpful for persons with mild to moderate Alzheimer's disease (6–12 mg daily or 9.5 mg daily transdermally). The drug's cholinergic effects were expectedly linked to any side effects that were experienced.

5.3 Tyrosine kinase inhibitor

Masitinib

A total of 2 trials met the inclusion criteria of the review. According to the primary endpoint of the ADAS-cog, masitinib (4.5 mg/kg/day) (n=182) showed a significant benefit over placebo (n=176), with results of 1.46 (95% CI [2.46, 0.45]) (representing an overall improvement in cognition) versus 0.69 (95% CI [0.36, 1.75]) (representing increased cognitive deterioration), respectively, and a significant between-group difference of 2. The between-group difference for the ADCS-ADL primary endpoint was 1.82 (97.5% CI [0.15, 3.79]); p=0.038 (i.e., 1.01 (95% CI [0.48, 2.50] (indicating improved overall functional state) against 0.81 (95% CI [2.36, 0.74] (representing worsened functional state), respectively). Safety was in line with the known side effects of masitinib (maculopapular rash, neutropenia, and hypoalbuminemia). The independent parallel group's titrated masitinib 6.0 mg/kg/day versus placebo efficacy results (n=186 and 91 patients, respectively) were equivocal, and there was no new safety signal seen. People with mild to severe AD may benefit from using masitinib (4.5 mg/kg/day).

5.4 Monoclonal Antibodies

Aducanumab

A total of 10 trials met the inclusion criteria of the review. A total of The poll was completed by 1025 respondents in total. Auranumab was initially new to around three-quarters of the respondents, but after being informed of the drug's possible clinical and financial effects, respondents were less in favor of the drug's approval. 63 percent of respondents are in favor of only allowing those who are most likely to benefit from aducanumab access. Sixty-five percent said they would be willing to enroll a family member in a randomized placebo-controlled trial, while seventy-one percent said they would be willing to do so for a relative with moderate Alzheimer's disease. 81 percent concur that aducanumab should be taken off the market if confirmatory trials are unsuccessful. Acuranumab coverage would cost an additional $1 to $5 in Part B rates, according to the median response. Findings show support for a number of suggested policies in response to the approval of aducanumab. When creating policies in reaction to aducanumab's approval, the viewpoints of an informed public should be taken into account.

Lecanemab

Lecanemab 10 mg/kg twice a week showed dose-dependent decreases in brain amyloid evaluated by PET, alterations in plasma biomarkers, and a reversal of cognitive deterioration at 12 and 18 months of treatment in the core. Lecanemab and placebo individuals both saw similar rates of clinical progression throughout this time, and clinical treatment differences persisted after dosage was stopped for an average of 24 months. Plasma A42/40 ratio and ptau181 levels returned to pre-randomization values during the gap more quickly than amyloid PET. Amyloid plaques were significantly reduced after receiving lecanemab therapy, and the rate of clinical decline was also slowed. The possibility of using plasma biomarkers to track the effects of lecanemab treatment is suggested by the data, which also show that rapid and dramatic amyloid reduction correlates with clinical benefit and possible disease-modifying effects.

5.5 Aggregation inhibitor

Hydromethylthionine mesylate

A total of 3 trials met the inclusion criteria of the review. Only A modified delayed-start open-label treatment phase 3 lasting 12 months follows a 12-month double-blind, placebo-controlled phase in this trial. In March 2022, 446 participants are anticipated to have finished the 12-month placebo-controlled phase. The data will offer confirmation of the clinical and biomarker advantages of hydromethylthionine mesylate in mild to moderate AD if the primary end goals are satisfied. It would likely enhance AD care because low-dose oral hydromethylthionine mesylate is straightforward to administer clinically, does not result in amyloid-related imaging abnormalities, and has a favorable

safety profile. With no ARIA risk, hydromethylthionine has the potential to be a short-term oral tau-based substitute for intravenous amyloid-based treatments. It is expected that low-dose oral hydromethylthionine mesylate would enhance AD care because it is straightforward to administer therapeutically, does not result in amyloid-related imaging abnormalities, and has a benign safety profile.

5.6 Endogenous antioxidant

Sodium benzoate

A total of 2 trails met the inclusion criteria. In the ADAS-cog (p=0.0021, 0.0116, and 0.0031 at weeks 16, 24, and endpoint, respectively), additional cognition composite (p=0.007 at endpoint), and CIBIC-plus (p=0.015, 0.016, and 0.012 at weeks 16, 24, and endpoint, respectively), sodium benzoate produced better improvement than placebo. Without any obvious adverse effects, sodium benzoate was well tolerated. Although not substantially (p=0.195), the sodium benzoate group's dropout rate (3.3%) was generally lower than the placebo group's (16.7%). With a mean dose of 525 and 716 mg/day, respectively, sodium benzoate demonstrated superior effectiveness over placebo at weeks 16 and 24. Sodium benzoate was accepted satisfactorily.

5.7 Supplementation

Only 3 trials met the inclusion criteria. 632 people with mild to moderate AD were enrolled in three comparable randomized, placebo-controlled trials that looked at omega-3 PUFA supplementation over the course of six, twelve, and eighteen months. There was no research that looked into different forms of dementia. Each trial had excellent methodological standards. The majority of the outcomes had high overall quality evidence. Omega-3 PUFA supplements' effectiveness in treating mild to moderate AD was not supported by any strong evidence, according to our research. All outcomes important to dementia patients had the same result.

5.8 Discussion.

The cellular stage of Alzheimer's disease occurs concurrently with the buildup of amyloid, which causes the spread of tau pathology. More than 40 genetic risk loci for Alzheimer's disease have previously been found, and APOE alleles have the strongest correlation with the disease. Heritable variables account for 60–80% of the risk of developing Alzheimer's disease. New data support the microbiological hypothesis that the neuropathology of AD is influenced by neurotropic members of the Herpesviridae family, particularly Human herpesvirus 1 (HHV-1), Cytomegalovirus (CMV), and Human herpesvirus 2 (HHV-2). Spirochetes and periodontal pathogens such as Porphyromonas gingivalis and Treponema denticola, which can lead to chronic periodontitis and may be a factor in the development of AD clinically. Impaired TGF-β1 signalling can cause alzheimer's disease. Systemic inflammation brought on by experimental periodontitis changed neuroimmune responses, tau phosphorylation, behavior, and cognition, increasing the risk of AD. Understanding the pathogenesis of sAD and modelling AD in vitro may benefit from using iPSC lines. With the use of these freshly developed sAD-hiPSC lines, new therapy targets for sAD and other hyperphosphorylated Tauopathies can be found and developed. In TOMM40 exonic variations, mutant TOMM40 (F113L) or (F131L) associated with AD causes neurotoxicity of hippocampus neurons by triggering microglia activation, NLRP3 inflammasome activation, and pro-inflammatory cytokine production.

A promising and rapidly developing field of study for diagnosing Alzheimer's disease is neuroimaging. Multiple brain imaging techniques, such as PET, MRI, and CT scans, which are regarded as screening exams for disease, can be used to identify abnormalities in the brain. Each scan uses a different technique to find specific abnormalities and structures in the brain and related areas. The use of 7-T MRI in the identification of microinfarcts shows promise and may help clarify the connection between cerebrovascular health and the course of AD. CT scans can reliably identify AD while also excluding other potential explanations of the symptoms. The mRNA expression of ABCA7 and SNCA demonstrated high to exceptional diagnostic specificity for AD. The National Institute on Aging and Alzheimer's Association (NIAAA) revised the diagnostic standards for Alzheimer's disease, and the use of amyloid biomarker tests, such as 18F-florbetapir, may increase confidence in the identification of mild cognitive impairment (MCI) brought on by Alzheimer's disease. The study didn't advise routine use of 18F-florbetapir PET in clinical practice to predict the transition from MCI to ADD despite the fact that sensitivity was good in one included study due to the poor specificity and the scant amount of data in the literature. Given the high cost of the 18F-FDG PET scan, it is essential to formally establish its accuracy and standardize the 18F-FDG PET diagnostic modality technique. The exploration of the 11C-PIB-PET biomarker is expensive. Cannot advise the regular use. the utility of CSF testing for tau, ptau, or the tau/ABeta ratio for the diagnosis of Alzheimer's disease in current

clinical practice is questionable. A 2019 study found that the MoCA-BC orientation test has strong sensitivity and specificity for identifying MCI, mild AD, and moderate-severe AD. Although it is now uncommon for Alzheimer's disease testing to include brain imaging, recent clinical studies have generated hopeful results that may change how doctors currently make the diagnosis. despite thorough and successful research over a lengthy period of time.

There is fair-quality evidence that donepezil treatment for 12 or 24 weeks leads to modest improvements in daily living skills, clinically assessed overall clinical state, and cognitive function in patients with mild, moderate, or severe dementia brought on by Alzheimer's disease. A cholinesterase inhibitor rivastigmine, it seems beneficial for people with mild to moderate Alzheimer's disease. (6–12 mg daily or 9.5 mg daily transdermally). Any side effects were expectedly related to the cholinergic effects of the medication. A tyrosine kinase inhibitor, its safety was in line with the known side effects of masitinib (maculopapular rash, neutropenia, and hypoalbuminemia). A monoclonal antibody aducanumab has recently got the approval of FDA but there are concerns regarding auranumab's negative effects in addition to questions about its efficacy. Acuranumab's main side effects have included edema and microhemorrhages, which are amyloid-related imaging abnormalities (ARIA). 41.3% of study patients who received higher-dose aducanumab medication made up ARIA. About 25% of those with ARIA reported having accompanying symptoms such headaches, confusion, dizziness, and nausea. The data also reveal that rapid and substantial amyloid reduction correlates with clinical benefit and possible disease-modifying effects, suggesting the prospect of employing plasma biomarkers to monitor the effects of lecanemab treatment. Oral hydromethylthionine mesylate would probably improve AD therapy because it is easy to deliver therapeutically, does not result in amyloid-related imaging abnormalities, and has a favorable safety profile. At weeks 16 and 24, sodium benzoate showed better effectiveness than placebo, with a mean dose of 525 and 716 mg/day, respectively. Benzoate sodium received favourable responses. Alkaloids, steroids, terpenoids, flavonoids, and polyphenols are examples of naturally occurring anti-inflammatory substances with the potential to prevent and treat AD symptoms that are also widely bioactive, less toxic, readily available, and adaptable. No convincing evidence was found for the usefulness of omega-3 PUFA supplementation in the treatment of mild to moderate AD.

Chapter Six

Conclusion

6. Conclusion

With the aging of the population, AD has become an urgent issue for social public health, bringing a huge burden to individuals and society. A large number of studies have proposed various hypotheses on the etiology and pathological state of AD, providing valuable information for multi-target treatment of AD. Unfortunately, the current clinical use of anti-AD drugs can only delay the symptoms of AD patients, and cannot cure AD. The relationship between systemic inflammation. Impaired TGF-β1 signalling, microbiological hypothesis and AD may provide a new strategy for discovery and development of novel agents to treat AD. Understanding the pathogenesis of sAD and modelling AD in vitro may benefit from using iPSC lines. To find abnormalities in the brain, a variety of brain imaging methods can be utilized, including PET, MRI, and CT scans, which are thought of as screening tests for disease. This study found information from some trials of 18F-florbetapir, 11C-PIB-PET, (18)F-FDG PET for the diagnosis of AD. But the majority of the studies claimed that the accuracy, specificity and the sensitivity were poor. It's difficult for routine use due to high cost. This study found The MoCA-BC orientation test has a high sensitivity and specificity for detecting MCI, mild AD, and moderate-severe AD, according to a 2019 study. To improve an early diagnosis of Alzheimer's disease dementia, future research should concentrate on combinations of biomarkers rather than one single biomarker.

This study revealed many major class of drug like cholinesterase inhibitors, tyrosine kinase inhibitor, monoclonal antibodies, aggregation inhibitors, endogenous antioxidant which are beneficial to treat mild to moderate AD. But most of the drug have less safe and efficient. Several studies have confirmed about the side of effect the drug. Only Oral hydromethylthionine mesylate has a favorable safety profile. Further study need to find out the exact causes, diagnosis procedure and safe and effective drug for the treatment of AD.

Chapter Seven

Reference

7. Reference:

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