Marine Compounds in the Treatment of Alzheimer's Disease

By

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Bachelor of Pharmacy (Hons.)

Department of Pharmacy
Brac University
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Declaration

It is hereby declared that

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2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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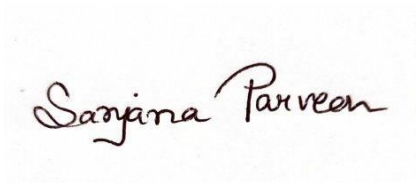

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Approval

The project titled “Marine compounds- a new hope for Alzheimer’s Disease” submitted by Sanjana Parveen (17346003) of Summer, 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on March 10 ,2022.

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Ethics Statement

This study does not involve any human or animal trial.

Abstract

Brain shrinkage and cell death occurs due to Alzheimer's disease, a degenerative neurologic illness. Memory loss, social and behavioral deterioration, and the inability to operate independently are all symptoms of Alzheimer's disease, which is the most frequent cause of dementia. The accumulation of beta amyloid plaque and neurofibrillary tangles are the hallmarks of alzheimer’s disease and conventional treatments only aim to soothe symptoms rather than treat or prevent disease. Presently, the scientific community is working together to find innovative natural compounds that are helpful against Alzheimer's disease and marine natural products have been demonstrated to be potential possibilities. Currently bryostatin-1, homotaurine, dictyostatin, docohexanoic acid, rifampicin, gracilins are being tested for alzheimer’s disease. More clinical trials need to be conducted for marine compounds to be used in alzheimer’s patient. Along with that combination therapy consisting of marine compounds have a prospect of displaying better activity that need to be tested.

Keywords: Alzheimer’s disease, Marine compounds, Bryostatin-1, Homotaurine, Dictyostatin, Docohexanoic acid.

Dedication

Dedicated to my teachers, family and friends.

Acknowledgement

First of all, I would like thank my Almighty Allah, for allowing me to finish my undergraduate thesis in perfect health and with bravery and wisdom. I would want to express my gratitude to my parents and my only brother Labib Abdullah Ishmam for their support and encouragement during the most challenging periods of my life. Also, I would like to thank Dr. Hasina Yasmin, Deputy Chair, Department of Pharmacy, Brac University, for her constant support, direction, constructive criticism and comments over the course of my thesis. Moreover, I would like to thank Professor Dr. Eva Rahman Kabir, Chairperson, Department of Pharmacy, Brac University for always being willing to lend a hand. Lastly, I would like to thank all my faculty members, batch mates and family members for making my academic life easier and memorable.

Table of Contents

List of Figures

List of Acronyms

AD	Alzheimer's Disease
APP	Amyloid Precursor Protein
MCI	Mild Cognitive Impairment
PET	Positron Emission Tomography
IWG	International Working Group
GERD	Gastroesophageal Reflux Disease
NFT	Neurofibrillary tangles
BDNF	Brain-derived Neurotrophic factor
MMSE	Mini-Mental State Examination
CSF	Cerebrospinal Fluid
DHA	Docosahexanoic Acid
AEs	Adverse Event
ROS	Reactive oxygen Species
MMP	Matrix Metalloproteinase
SP	Senile Plaque
PCG	Posterior Cingulate Gyrus
ERK	Extracellular Regulated Kinase
PUFA	Polysaturated Fatty Acid

Chapter 1

Introduction

1.1 Alzheimer’s disease in brief

Alzheimer's disease is a form of brain illness that progresses over time and grows more severe. A person's risk of developing Alzheimer's disease increases by 20 years or above before symptoms appear. It all begins with changes in the brain that are invisible to the individual who is being impacted. Individuals only start to notice apparent symptoms like loss of memory, language difficulties, and other cognitive difficulties after years of brain changes (“2021 Alzheimer’s Disease Facts and Figures,” 2021). It was in 1907 that Alois Alzheimer published his case study of a 51-year-old lady who had been experiencing memory loss that was progressing at an alarming rate in addition to mental symptoms (Castellani et al., 2010). More than 50 million people worldwide are already diagnosed with Alzheimer's disease (AD). This figure is expected to be doubled every five years and by 2050 will reach 152 million. A proper solution for Alzheimer's disease does not exist currently; however, therapies present that at least relieve the symptoms (Breijyeh & Karaman, 2020). Cognitive and functional abilities deteriorate as the disease advances due to a loss in the capacity to retain new knowledge. As a result, the first neurons to be injured and killed are typically found in areas of the brain where new memories are being formed (Gaugler et al., 2016). Delaying and eventually reversing the progression of Alzheimer's disease will require early identification, say researchers. There has been a remarkable increase in early detection studies in the recent decade (Sperling et al., 2011). Three factors can be specified as risky in case of late-onset AD such as age (L. E. Hebert et al., 2010), APOE-e4 (Saunders et al., 1993) and also family history (Green et al., 2002). People with Alzheimer's disease in the United States in 2016, according to the Alzheimer's Association and data from Hebert and other researchers, pie chart has been shown below (Hebert et al.,

2013). In terms of Alzheimer's susceptibility, the APOE- e4 gene has the most significant influence. Protein transporting cholesterol in the circulation is a function of APOE-e4. Three variants of such ApoE gene are passed down from parent to child. When it comes to Alzheimer's disease, those who have the e4 version of ApoE are more likely to get the disease, but that does not mean that they will have Alzheimer's. If someone have the e2 version rather than the e3, risk will be lower. There is a three- to eight-fold more significant ("2021 Alzheimer's Disease Facts and Figures," 2021) risk of Alzheimer's disease in people who receive one duplicate of the e4 version than in those who receive two duplicates of the e3 version (Holtzman et al., 2012). Concerning beta-amyloid buildup (Jansen et al., 2015) and Alzheimer's, persons having the e4 version of APOE gene are much more prone than those in the other two forms to develop these conditions earlier in life (Spinney, 2014). Secretase degradation of APP produces a range of Ab peptides (Read & Suphioglu, 2019). There are two main types of Aβ peptides: Aβ42, which is mainly seen in distinct Aβ deposits, and Aβ40, which is more readily soluble and may appear later in the course of the disease (Miller et al., 1993). Additionally, in people with severe cerebral amyloid angiopathy, mutations inside Aβ coding area of APP might cause Aβ38 to accumulate in the vessel walls (Moro et al., 2012). Premature soluble peptide clusters, that vary depending on the mutant type, may also be responsible for the development of AD (Murphy & Levine, 2010). Gamma-secretase delivers PSEN towards the surface of the cell after endoproteolytic breakage and g-secretase complex assembly, which may influence APP synthesis (Honarnejad & Herms, 2012). Since the 42-specific Gamma-secretase of PSEN1 might be enhanced by mutant PSEN1, this could lead to a rise in the formation of amyloid-forming molecules (Li et al., 2016). The G-secretase function may also be reduced by PSEN, resulting in a loss of performance (De Strooper et al., 2012).

Recent findings point to a strong correlation between the condition of the cardiovascular system and the condition of the brain (Brain Health Is Connected to Heart Health | Cdc.Gov, n.d.). The brain receives nourishment from the most extensive blood arteries and thus in order to keep the brain provided well with the oxygen supply it requires (Scheuer et al., 2021). Many of cardiovascular events are also linked to an increased chance of developing dementia (Tini et al., 2020). Tobacco use and obesity in middle age are examples of these variables (Dementia and Heart Health: Are They Related? | Johns Hopkins Medicine, n.d.). Memory loss may be exacerbated by poor glucose metabolism, which is seen in diabetics but may be present in those without diabetes (Hanyu, 2019). Dementia is also linked to high blood pressure (High Blood Pressure and Dementia | Alzheimer's Society, n.d.) and excessive cholesterol in middle age (Abnormal Cholesterol Metabolism Linked to Dementia Risk | National Institute on Aging, n.d.).

1.2 Continuum of AD

The brain starts to experience significant new large-scale alterations, like brain shrinkage, whenever brain cells die as a result of neuronal loss (Hung et al., 2016). As seen in the illustration, the brain of someone suffering from Alzheimer's disease begins to shrink, a condition called as atrophy. The gyri portion of the brain, made up of distinctive grooves of the brain, becomes thinner as a result of atrophy. Lastly, the ventricles, which seem to be the fluid-filled chambers inside the brain, become larger and more rounded in shape (Ashrafian et al., 2021).

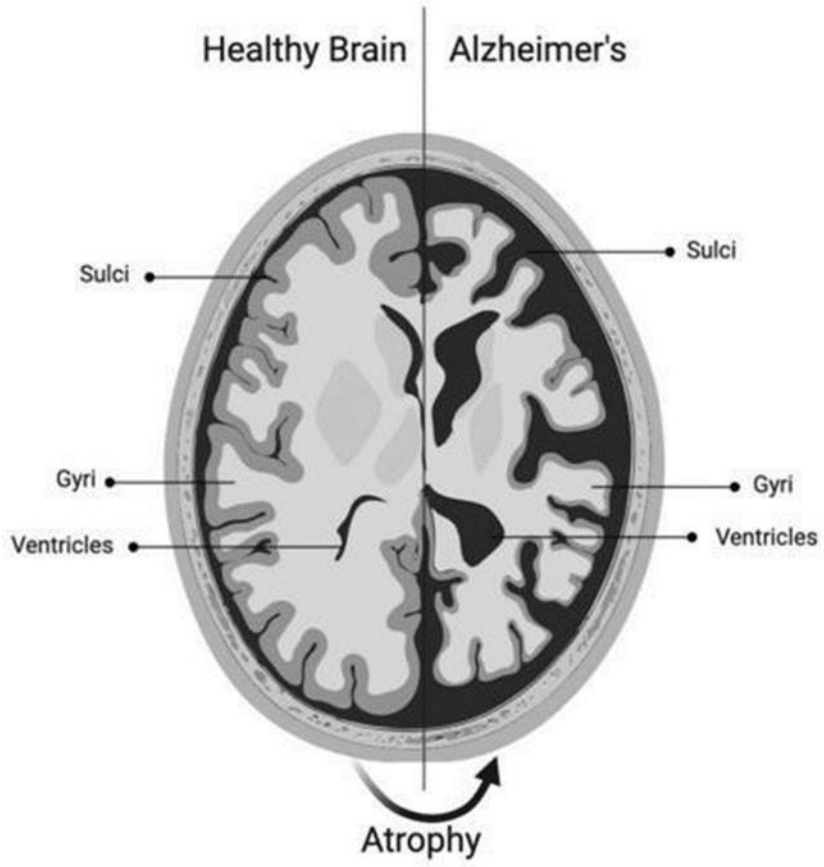

Figure 1: Atrophy development in Alzher's disease (Ashrafian et al., 2021)

More than 50 million people worldwide are already diagnosed with Alzheimer's disease (AD). Every five years this figure is expected to be doubled and reach 152 million in 2050. People, families, and businesses are all affected by the impact of Alzheimer's disease (AD). A remedy for Alzheimer's disease does not exist at the current time, however, there are therapies offered that at least relieve the symptoms (Livingston et al., 2020; Yiannopoulou & Papageorgiou, 2020).

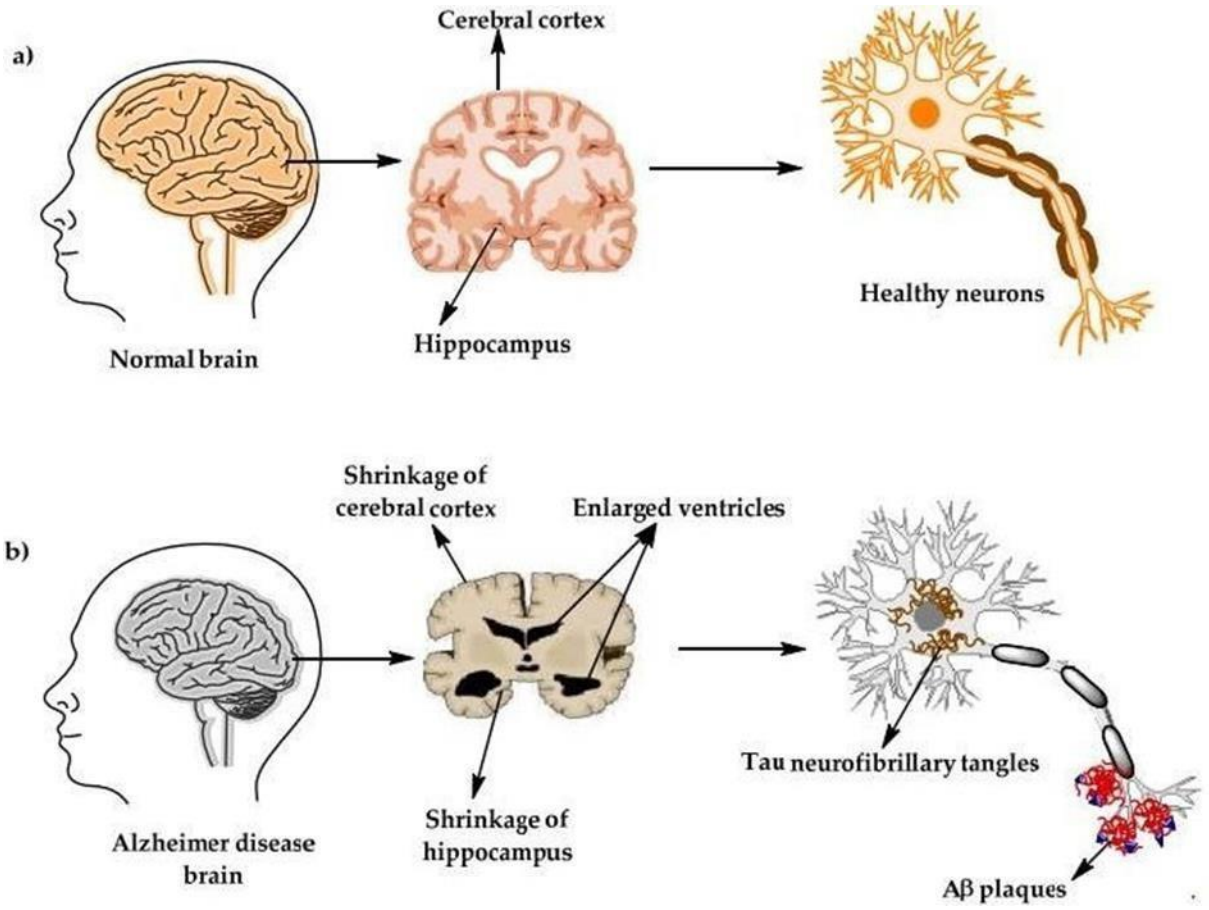

Figure 2: Physiological Structure of brain in AD (Breijyeh & Karaman, 2020)

A continuum of modifications in the brain leads to loss of memory and physical impairment in Alzheimer's disease. Preclinical Alzheimer's disease, mild cognitive impairment (MCI) caused by Alzheimer's disease, and dementia caused by Alzheimer's disease all fall within this continuum (Albert et al., 2013; "Defining the Preclinical Stages of Alzheimer's Disease: Recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic …," n.d.; McKhann et al., 2011). Individuals spend varying amounts of time at each point on the continuum. Age, heredity, gender expression, and other variables impact the length of each phase (Vermunt et al., 2019).

1.2.1 Preclinical Alzheimer's disease

As the condition progresses, indications like memory loss may begin to appear, although these changes are not yet visible to the naked eye (Dubois et al., 2016). Individuals without cognitive impairment who underwent postmortem review and showed signs of Alzheimer's disease plaques were the first preclinical Alzheimer's disease cases with in the late twentieth century (HUBBARD et al., 1990). Beta-amyloid abnormalities in PET (positron emission tomography) scans and CSF (cerebrospinal fluid) analysis are two examples of Alzheimer's disease biomarkers (Schipke et al., 2012; Vallabhajosula, 2011). Preclinical conditions have been categorized in a variety of ways. There are two distinct preclinical stages identified by the International Working Group (IWG): presymptomatic and asymptomatic (Dubois et al., 2016). Individuals with an autosomal dominant monogenic mutation, known as pre-symptomatic AD, are almost certain to acquire full-blown clinical Alzheimer's disease. With the help of mutation identification, a disease may be detected at any stage of development. There is a lot of debate over the "asymptomatic at-risk" condition. Early-onset- onset Alzheimer's disease symptoms are not required to be considered asymptomatic at risk. There is a new IWG definition of preclinical Alzheimer's disease, which specifies that there must be at minimum one biomarker showing Alzheimer's pathology to be considered preclinical (Dubois et al., 2016). It has been suggested that even in the lack of any clinical symptoms, the appearance of one sign of brain amyloidosis within CSF or PET may be enough to confirm the diagnosis of Alzheimer's disease. In light of this, persons having brain amyloidosis may be given disease-modifying medications in the future, even though there's no proof that all of these people will eventually acquire the illness. If amyloidosis is required for an AD diagnosis, another possibility is that it is not enough to accurately forecast whether the illness would eventually develop to a symptomatic stage. Amyloid plaque is found in the brains of many considerable numbers of people postmortem who had no signs of clinically manifested illness antemortem but whose

brains now fulfil neuropathologic clinical criteria for having the disease (McKhann et al., 2011; Vos et al., 2013). The brain adapts for the early alterations in Alzheimer's, allowing people to keep functioning normally ("2018 Alzheimer's Disease Facts and Figures," 2018). Those with indications of Alzheimer's-related brain alterations do not always start showing symptoms of mild cognitive impairment or dementia as a result of Alzheimer's (Bennett et al., 2006; Knopman et al., 2003)

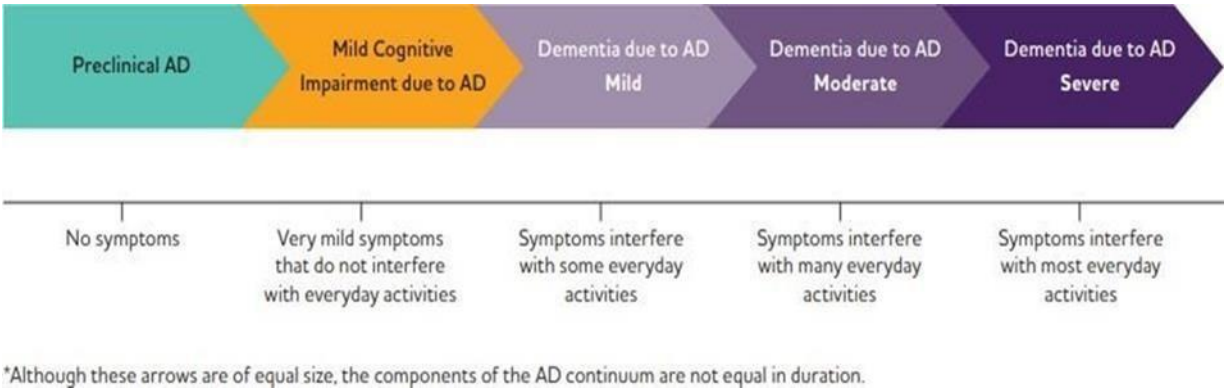

Figure 3: Continuum of AD ("2021 Alzheimer's Disease Facts and Figures," 2021)

1.2.2 Mild Cognitive Impairment

This is the mildest or earliest stage of Alzheimer's disease, when patients begin to experience a variety of symptoms, including difficulty with everyday activities due to memory loss and concentration problems, confusion about where they are in relation to time, and depression (Sannerud et al., 2016; Wattmo et al., 2016). People with MCI have quantifiable changes in cognitive abilities that are evident to those around them, but they do not impair their capacity to carry out their daily routines. MCI affects around 15% to 20% of persons over the age of 65 (Roberts & Knopman, 2013). After two years, roughly 15% of people with MCI acquire dementia (Petersen et al., 2018). In the five years following diagnosis, Alzheimer's disease develops in around a third of people with mild cognitive impairment (MCI) (Ward et al., 2013). As a reminder, some people are identified with MCI years later their cognitive deterioration

began, and these people are more likely to acquire dementia than those who are detected earlier. As a side aside, some people with MCI return to normal functioning or do not experience additional cognitive impairment after being diagnosed with MCI. It is possible to diagnose MCI incorrectly and restore cognitive alterations if, for example, a medicine induces cognitive changes by accident (“2018 Alzheimer’s Disease Facts and Figures,” 2018).

1.2.3 Dementia

It is important to note that symptoms of Alzheimer's disease-related dementia include impairment in everyday living, as well as biomarkers of Alzheimer's-related brain alterations. It is normal for people with Alzheimer's to encounter a wide range of symptoms which evolve over time. These symptoms are an indication of the extent of injury to the brain's nerve cells. This phase can be divided as mild dementia, moderate dementia and severe dementia depending on the intensity of the neuronal damage (“2021 Alzheimer’s Disease Facts and Figures,” 2021). When atrophy is developed within the brain, cerebrospinal fluid starts to fill up the space which was previously taken by the brain tissue. Loss of memory such as complexity remembering well-known words as well as uncertainty about familiar surroundings, a slowdown in the capacity to analyze complex ideas, for example, trouble balancing a cheque book or making a meal), and emotion and public persona modification are more pronounced in case of mild to moderate Alzheimer's disease (AD). Atrophy spreads to other parts of cerebral cortex (Morrison & Lyketsos, 2005). There are parts of the brain that are affected by the progression of the disease, which governs speech, thinking and the interpretation of sensory information. The patients with severe Alzheimer's disease observe decreased long-term memory, convulsions, urination, loss of weight, no identification of closed ones, difficulty to sit, which is related to the intensity of the level of brain shrinkage (Alzheimer’s DAlzheimer’s Disease Education and Referral Center Web Site. Alzheimer’s Disease—Unraveling the Mystery. - Google Search, n.d.; Forstl et al., 1995). This is the most

severe form of Alzheimer's disease and occurs when the disease has spread from one part of the brain, such as in the frontal or temporal lobe, to the full cortex area, likely to result in the gradual loss of cognition and physical abilities, which can eventually lead to the patient's death as a result of these complications (Apostolova, 2016; De-Paula et al., 2012).

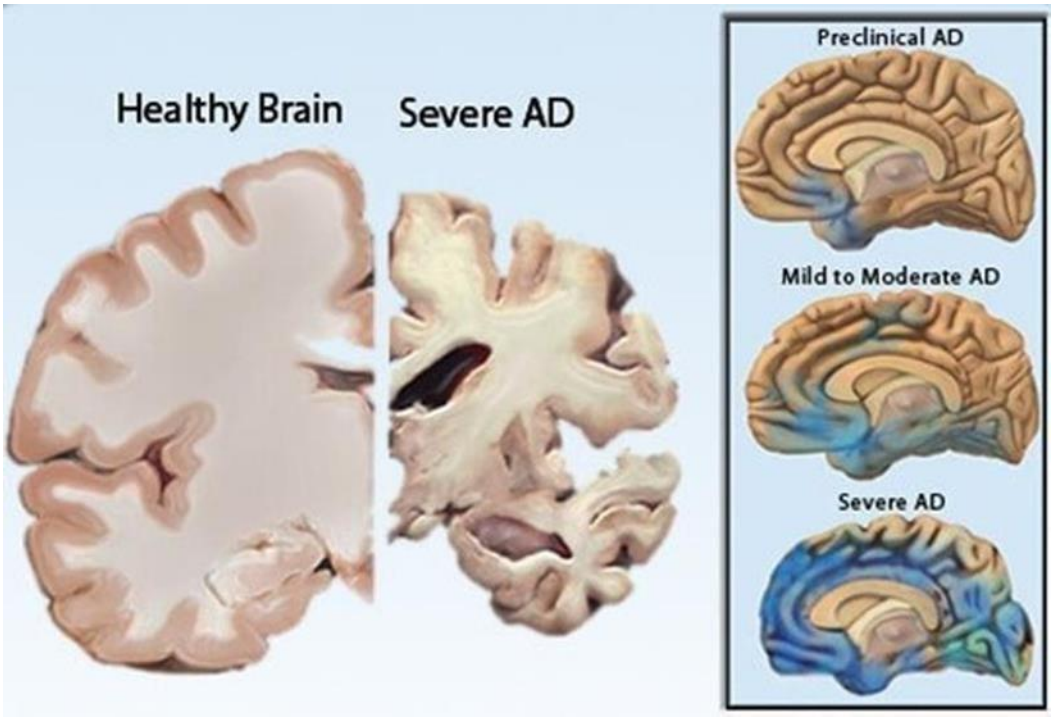

Figure 4: Structural representation of brain in AD (Alzheimer's Disease Picture Image on MedicineNet.Com, n.d.)

Each neuron in a normal healthy brain has a long, branching extension. Using these extensions, neurons can make connections with one another. At synapses, brief pulses of chemicals emitted through one neuron and recognized by some other neuron, information travels (Bartus, 2000). Synapses in the brain are estimated to number in the tens of trillions. The cellular foundation of memories, ideas, feelings and actions are created by the fast transmission of information across the brain's nerves and axons (Jensen, 2005). Two of the brain abnormalities linked with Alzheimer's disease include the buildup of the beta-amyloid protein into clusters outside the neurons and the formation of an aberrant form of the protein tau inside the neurons (Stein et

al., 2004). Beta-amyloid oligomers, which are tiny collections of beta-amyloid, may lead to deterioration and neuronal death by messing with the neuron-to-neuron transmission. Tau tangles impede the movement of nutrients and some other chemicals required for regular activity and the maintenance of neurons within the brain (Ittner & Ittner, 2018). Inflammation and atrophy are two of the markers of Alzheimer's-related cognitive decline (Sala-Llonch et al., 2017). These cells, which are part of the brain's immune system, are known as microglia and are activated by the development of beta-amyloid as well as tau proteins (Solito & Sastre, 2012). Toxic proteins and cellular debris are removed from dead and injured cells by microglia (Yeh et al., n.d.). Whenever the microglia can't control the amount of debris that has to be removed, chronic inflammation can develop. Cell death results in atrophy (Scott et al., 1992). A decline in the brain's capacity to process glucose, its primary source of energy, severely damages neurological function in Alzheimer's disease (Yao et al., 2011).

1.3 Drug discovery and marine compounds

When it comes to discovering novel medications and new molecules, our planet's natural environment has become an excellent source of chemicals. Bioactive chemicals from marine species have extended the scope of pharmacological study because of the growth of pharmacological resistance to established medicines and the challenges in treating numerous disorders (Cappello & Nieri, 2021). The polysaccharide alginate found in kelp in 1881 was the first marine substance employed in the treatment of gastroesophageal reflux disease (GERD) (Leiman et al., 2017). The seas cover more than 70 percent of the planet's land area, making them the planet's most extensive ecosystem and a rich source of biological and chemical variety. Many medicines, active compounds, and other substances generated from marine creatures have been discovered recently, even though earthly origins still account for the vast majority of pharmaceuticals. Over the past few years, the number of marine-derived compounds has increased from 30,000 to over 1,000 every year, with the majority of these new

compounds found after 2008 (Kiuru et al., 2014). About half of the medications put on the marketplace in the previous two decades were generated directly from tiny compounds of natural sources (Alonso et al., 2005). One of the issues with marine substances is the difficulty in synthesizing their complicated chemical compositions and the limited amounts available from their native sources (Rubiolo et al., 2014). As new sample collecting techniques and spectroscopy techniques and isolation procedures have already been established, there has been an increase in the investigation of the marine ecosystem (Martins et al., 2020). While marine substances have significant limits, novel chemical configurations with intriguing therapeutic qualities, like anti- inflammatory, analgesic, immunomodulatory, neuroprotective, and antitumor are being discovered as a result of increased research (Alonso et al., 2005; Choi & Choi, 2015). In this article bryostatin-1, homotaurine, rifamycin, dictyostatin, docosahexaenoic acid and gracilin molecules are discussed as a mean of Alzheimer's disease treatment.

1.4 Rationale of the study

Alzheimer's disease (AD) is a global epidemic which is rapidly advancing. Genetically complicated, slow-progressing, and irreversible are the characteristics of Alzheimer's Disease (AD), which affects the brain's neurons (Hampel et al., 2011). In 2001, 24 million individuals over the age of 60 were believed to have dementia, which is expected to increase per 20 years and impact over than 80 million individuals worldwide in 2040 (Ferri et al., 2005). The expected rise in Alzheimer's disease (AD) incidence is a direct result of the aging population, particularly in poor and mid nations. Thus, the proportion of individuals with dementia is likely to climb by 80– 190% in Europe, North America, and the industrialized Western Pacific area from 2001 to 2040, whereas in Latin America, India, China, and North Africa and the Middle Eastern Crescent, a rapid increase of more than 300% is predicted (Hampel et al., 2011). Till now FDA approved five drug to treat the AD symptoms and recently one drug has been approved for delaying clinical condition (U.S. Food and Drug Administration, n.d.).

Compounds with unusual and distinctive chemical properties found in the marine ecosystem have shown to be a valuable resource for the structural modeling as well as chemical manufacturing of novel medications with increased effectiveness and uniqueness (Alves et al., 2018). So, depending on this information it can be stated that marine compounds can play a vital role in case of producing Alzheimer's disease specific drug because of its potentiality.

1.5 Aim of the study

The aim of the study is to clearly correlate the ability of some marine-derived compounds in case of treating Alzheimer's disease along with their status in clinical trials.

Chapter 2

Pathophysiological Hallmarks

2.1 Beta-amyloid plaque

2.1.1 Beta-amyloid plaque in brief

Though the pathogenesis and specific reason for causing Alzheimer's disease is still unclear, beta- amyloid plaque is considered one of the core components in the case of detecting Alzheimer's disease (Ismail et al., n.d.). A protein amyloid produced out of a bigger precursor molecule called APP ultimately aggregates with one another and forms a plaque known as beta-amyloid plaque (Murphy & Levine, 2010).

2.1.2 Formation of beta-amyloid plaque

APP, known as amyloid precursor protein, is mostly found in the brain's neuronal and glial cells and where APP is a transmembrane protein having a big extracellular N-terminal domain, and a briefer cytoplasmic C-terminus (Reinhard et al., 2005). Besides, there are three enzymes called alpha-secretase, beta-secretase, gamma-secretase. Usually, alpha-secretase cuts at a specific area of APP and creates a peptide fragment; on the other hand, gamma-secretase also cuts at a specific area of APP and creates another peptide fragment (Madav et al., 2019). APP is cleaved by alpha- secretase enzyme, as a result soluble APP alpha (N terminal fragment) and alphaCTF (C terminal fragment) are formed. After that alphaCTF which remains on the membrane dissociates into p3 peptide and AICD (APP intracellular domain) by gamma-secretase (Bergström et al., 2016). This is called the non-amyloidogenic pathway (Takahashi et al., 2017). This soluble component enhances neuroplasticity, controls neuron responsiveness, and shields neurons against oxidative as well as metabolic stress (Madav et al., 2019). On the other hand, APP is cleaved by beta-secretase at a wrong site, which results in

soluble APP beta keeping a C- terminal fragment in the membrane, which is cleaved by gamma-secretase (Bergström et al., 2016). This is called the amyloidogenic pathway (Takahashi et al., 2017). Consecutively β secretase and γ secretase enzymes cleave and produce the extracellular Aβ42 portion monomers (Bolduc et al., 2016; Pasternak et al., 2004; Sannerud et al., 2016). As a result, peptides of 38-42 amino acids are formed known as Aβ42 or Aβ which are insoluble in nature and start to stick with each other and form a recognizable cluster known as beta-amyloid plaque (Bergström et al., 2016).

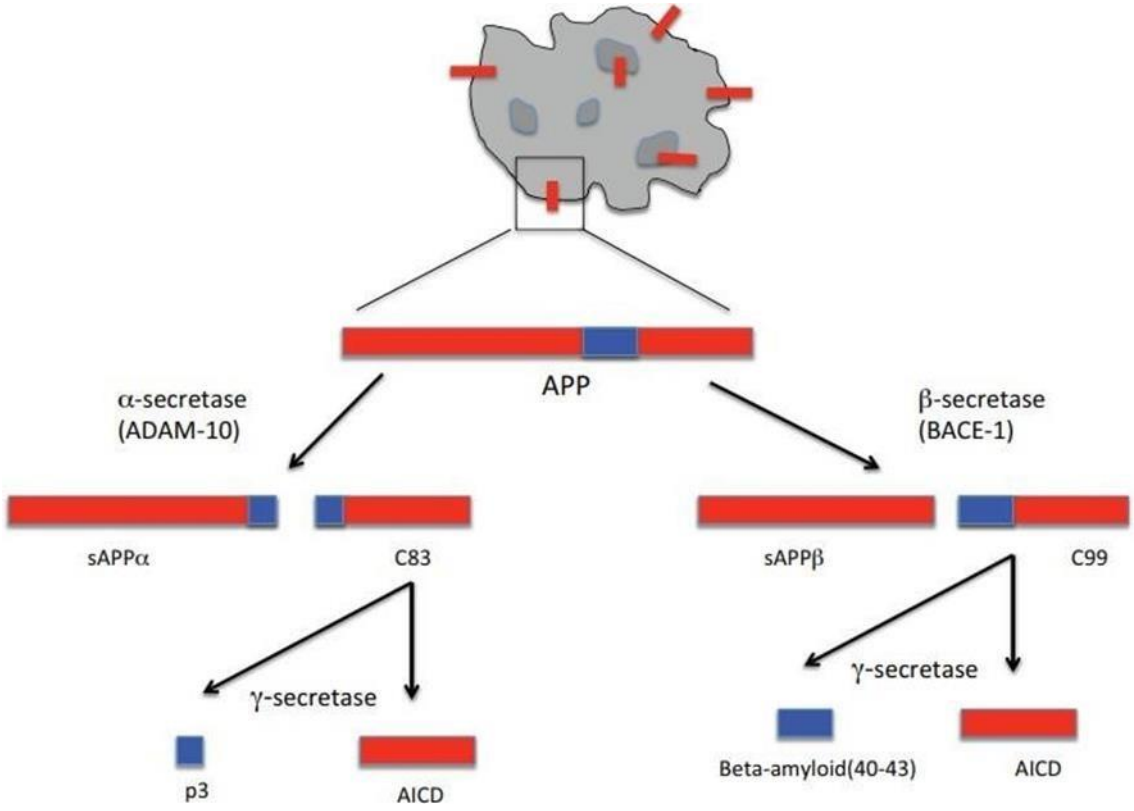

Figure 5: Process of forming beta-amyloid from APP (Humpel, 2017)

2.1.3 Difficulties associated with Beta-amyloid plaque

This beta-amyloid, also known as senile plaque, remains outside the neuron and activates immune response, which undergoes complement system and inflammation occurs (Leong et al., 2019). So, what happens is that the neurons start to get damaged and become unable to

function correctly. Also, these beta-amyloid plaques start to accumulate in the synaptic cleft and hamper synaptic transmission (Madav et al., 2019).

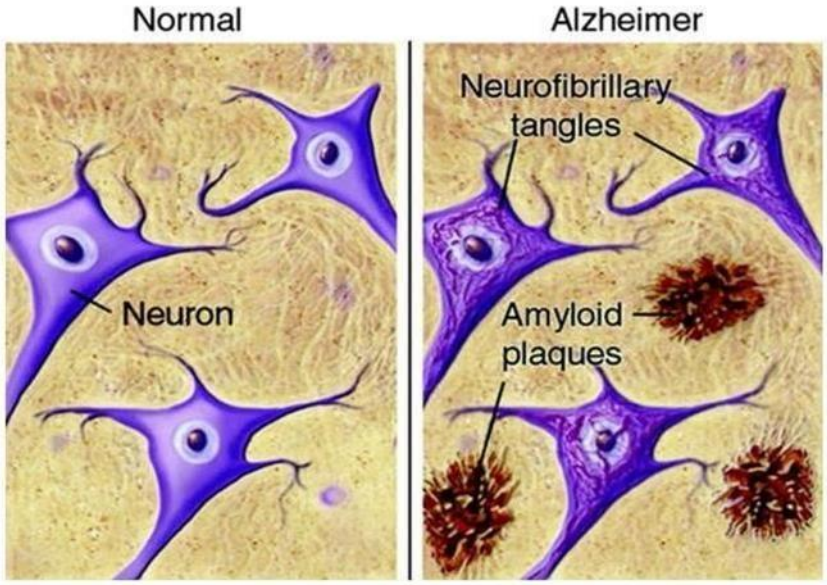

Figure 6: Neuronal representing extracellular beta amyloid plaque and intracellular neurofibrillary tangles (Mcgirr et al., 2020)

When cells produce b-amyloid, the molecule remains loose and spread. When these b-amyloid molecules start to fold, it is known as the "b-folded pattern" which can be caused by different factors and create a sheet like structure called beta sheet (Olsson et al., 2018). Basically, two or more β-amyloid molecules form a dimer, tetramer, oligomer cluster, and starts to adhere to synapses, damage neurons, and prevent long-term stimulatory effects from occurring, as a result, β-amyloid fibrils and plaques are formed as more β-amyloid molecules join together, producing an aggregation (Seeman & Seeman, 2011). Sole molecules regarding β-amyloid-42 partake a natural tendency to duos with one another to arrange a trimer otherwise a dimer or a cumulative of numerous b-amyloid particles to form amyloidal plaques. This coupling process looks to take place inside humanoid neurons (Seeman & Seeman, 2011). As soon as Amyloid-beta plaque generates, they might create at least three main difficulties in the cell. Amyloid-beta plaque can stay among two well neurons and hamper the signaling procedure between

them. Brain injury and loss of memory will occur when neurons stop sending messages at the proper moment. If ABP causes inflammation, it may harm the adjacent neurons as well through its natural response. It is possible for ABPs to build up on the outside of blood vessels, called angiopathy. Hemorrhage or vascular rupture will eventually result from angiopathy (Ashrafian et al., 2021).

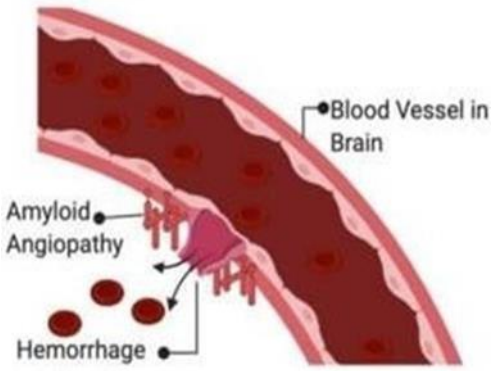

Figure 7: Hemorrhage due to angiopathy (Ashrafian et al., 2021)

The number of amyloid plaques does not appear to be correlated with dementia severity; however, the single type of β-amyloid molecules and their dimers and trimers are linked to the degree of dementia (Seeman & Seeman, 2011). In the early stages, beta amyloid peptides released as monomers are largely harmless; nevertheless, they progressively aggregate into hazardous oligomers and eventually aggregate as amyloid plaques in the end (Chasseigneaux & Allinquant, 2012).

2.1.4 Beta-amyloid plaque and microglia

Macrophage-like cells that are widely distributed throughout the adult brain and spinal cord where Microglia makes about 10-15% of the CNS' overall cell population. Microglial cells, like macrophages throughout the body, use phagocytic as well as cytotoxic methods to eliminate foreign substances. Additionally, microglia can play a role in inflammation and

homeostasis by releasing cytokines as well as other signaling particles (Cai et al., 2014). During Alzheimer's disease, the brain's microglia are unable to remove waste and protein accumulations, particularly beta-amyloid deposits, from the brain. In Alzheimer's disease, researchers are striving to discover why microglia are unable to execute this critical role. When plaques or other neuronal debris accumulate, a certain kind of glia called astrocytes is activated to assist in their removal. When such microglia gather near neurons, they are unable to execute normal debris-removing role rather promotes chemical substances to create further inflammation and harm neuronal cells in steading of being protective (What Happens to the Brain in Alzheimer’s Disease? | National Institute on Aging, n.d.). To sum up, the development of beta-Amyloid plaques in the brain is a hallmark of Alzheimer's disease (Sierra-Fonseca & Gosselink, 2018).

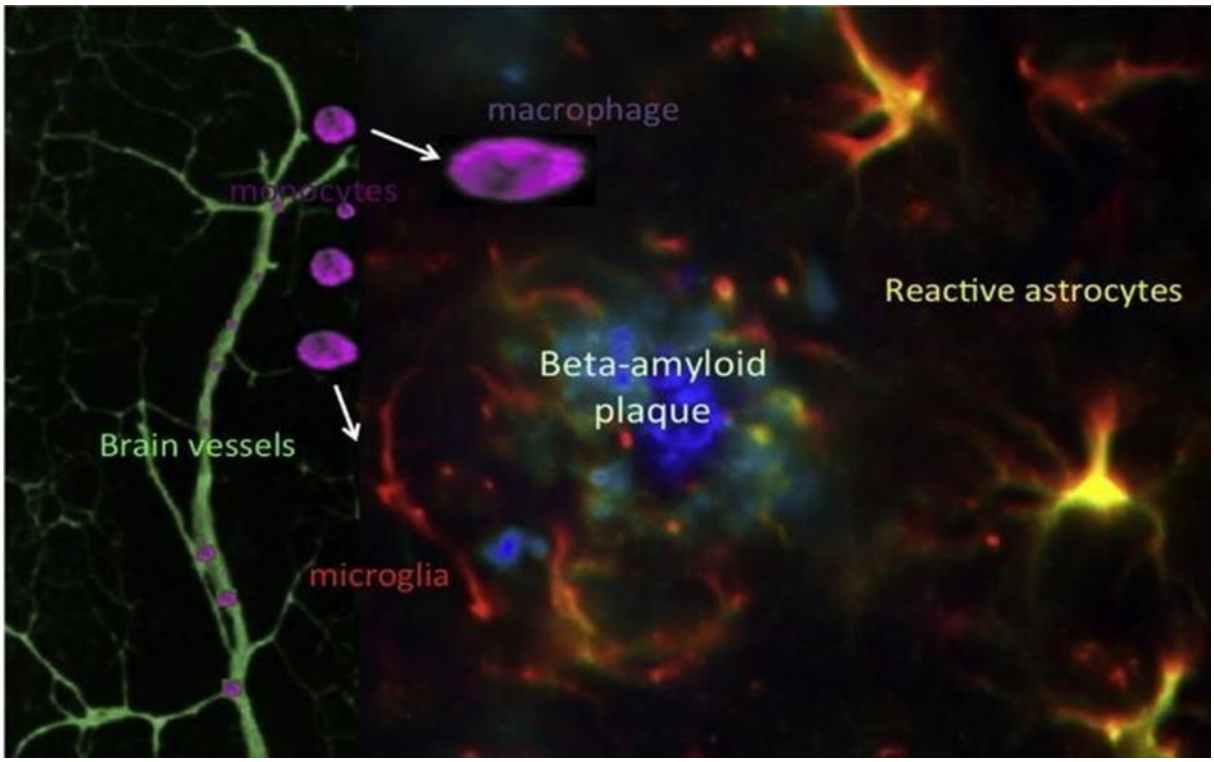

Figure 8: Activation of microglia due to Beta amyloid plaque (Hohsfield & Humpel, 2015)

2.2 Neurofibrillary tangles

2.2.1 Neurofibrillary tangle in brief

Tau protein-modified neurofibrillary tangles characterize Alzheimer's disease (Jouanne et al., 2017). Tau proteins are the primary components of the tangles that cause Alzheimer's disease. When the tau protein becomes hyperphosphorylated, it starts to aggregate by sticking to one anotherand forms neurofibrillary tangle (Perl, 2010).

2.2.2 Formation of neurofibrillary tangles

Neurons are the brain's basic components, and the space between them is known as a synapse, where neurotransmitters are exchanged. The tau protein stabilizes microtubules at normal synapses by binding the alpha and beta tubulin subunits (Gao et al., 2018). Intrinsically disordered Tau proteins are the most common microtubule-associated proteins in the brain. The central nervous system (CNS) is home to a large number of these proteins, which play a key role in the integrity of microtubules in axons astrocytes. Genomic integrity and cell signaling pathways are regulated by Tau proteins, which play a key role in these processes (Michalicova et al., 2020). Neurons in the brain lose some of their ability to remove waste material as they age. Protein, lipids, and diverse waste products such lipofucin accumulate inside neurons over time, causing inflammation and neuronal dysfunction. Tau produces oligomers when it binds to lipofucin. Tau alters its structure and develops a hairpin configuration, causing microtubule instability (Park et al., 2018).

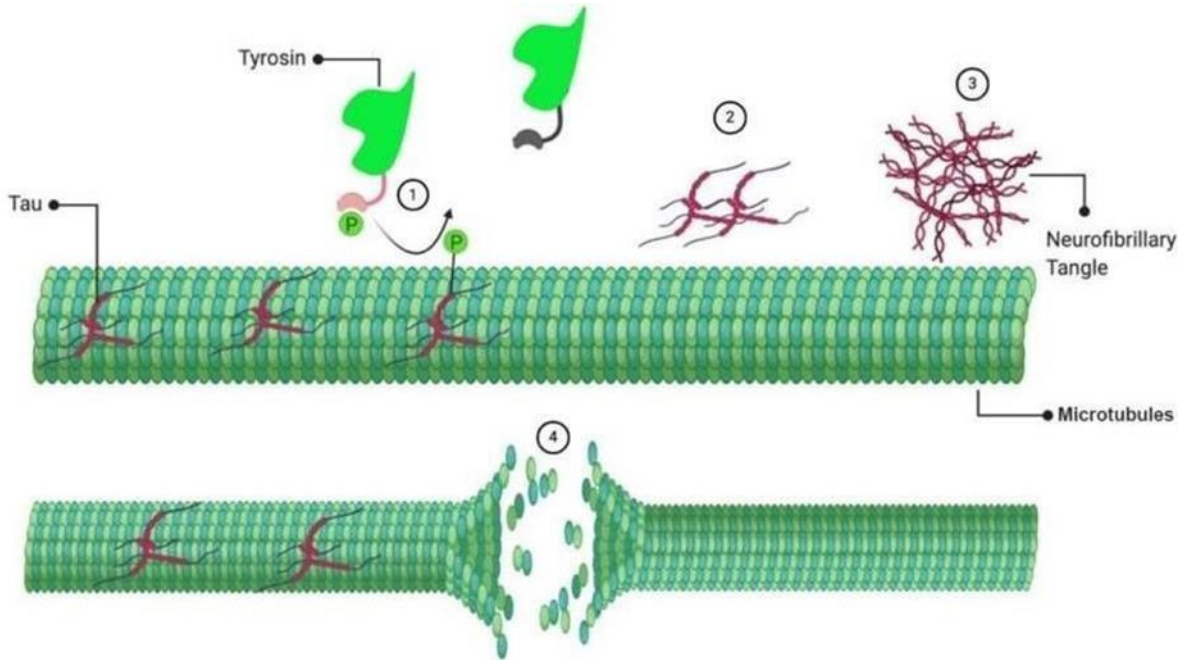

Figure 9: Generation of neurofibrillary tangles (Ashrafian et al., 2021)

Microtubules are one of the most essential aspects of the cytoskeleton that determines proper shape and gives mechanical stability to neurons, Tau protein is involved in their formation specially in case of stability. Phosphorylation of tau regulates tubulin binding, which is generally controlled by the combination approach of kinases and phosphatases. As a result of aberrant phosphorylation of the tau protein, which causes microtubule disruption in AD, this protein also self-polymerizes and aggregation takes place which ultimately generate NFTs, under these pathological settings (Kolarova et al., 2012). Amyloid beta plaques that are generated in the extracellular areas, according to the research, stimulate an internal signaling pathway within cells that results in their activation. Activated kinases handover a phosphate group towards tau protein, as a result, phosphorylated tau takes leave from microtubule (Ashrafian et al., 2021). To keep the cytoskeleton well-organized during the axonal process, the typical job of tau protein in AD is useless because this protein loses its ability to connect to microtubules (Kolarova et al., 2012). Microglia activation paves the way for tau aggregation and increases tau hyperphosphorylation through cytokine release, leading to the production of NFTs in transgenic Alzheimer's mice (Ismail et al., n.d).

2.2.3 Difficulties associated with NFTs

Intracellular diluted tangles obstruct impulse transmission, particularly around the axon area, neuronal cells gradually lose their function, resulting in degeneration and eventual demise (Madav et al., 2019). According to one theory, brain inflammation begins as a preventive reaction to dementia, where microglia try to engulf beta-amyloid fibrils; however, it doesn't happen and microglial activity falls. Later, when tau tangles develop, a damaging second stage of increased microglial stimulation develops, and this characteristic promotes the progression of the disease (Ismail et al., n.d.). Tau's ability to attach to microtubules and promote their formation is controlled by the phosphorylation of the protein. Tau must maintain a regular degree of phosphorylation in order to operate properly, but a hyperphosphorylated condition drop its biological activities (Kolarova et al., 2012). Neurons communicate frequently with each other in the brain. In order to transfer neurotransmitter molecules all over synapse, a neuron collects information from other neurons and creates an electrical signal that crosses the entire axon (Terry, 2000) but neurofibrillary tangles hinder this cell's transport mechanism, resulting in impaired synaptic communication and ultimately cell death occurs (What Happens to the Brain in Alzheimer’s Disease? | National Institute on Aging, n.d.). Brain regions that are affected by neurofibrillary tangles include the entorhinal and transentorhinal regions. At this point, these diseased entities expand to the hippocampus and neocortex, respectively (Tiwari et al., 2019).

2.3 Correlating Beta-amyloid plaque and NFTs

Another recent study demonstrated that removing tau from AD model mice protects against the deleterious consequences of beta amyloid plaque buildup but also questioned the concept that tau operates primarily downstream of beta-amyloid (Leroy et al., 2012). Human APP and presenilin-1 (PS1) mutants, each of which causes familial early-onset AD, were overexpressed

in the AD model mice. The APP/PS1 mice that had their tau genes spliced out were protected against memory loss, synapse loss, nerve cell loss, and premature mortality. However, this is in contradiction to past research (Hurtado et al., 2010; Leiman et al., 2017; Lewis et al., 2001). It was shown that tau- deficient APP/PS1 mice exhibited lower plaque loads than age-matched tau-expressing APP/PS1 animals (Lewis et al., 2001). Combined with past data showing beta-amyloid plaque is definitely influenced by tau, this new research suggests that tau has an impact on beta-amyloid plaque (Götz et al., 2001; Hurtado et al., 2010).

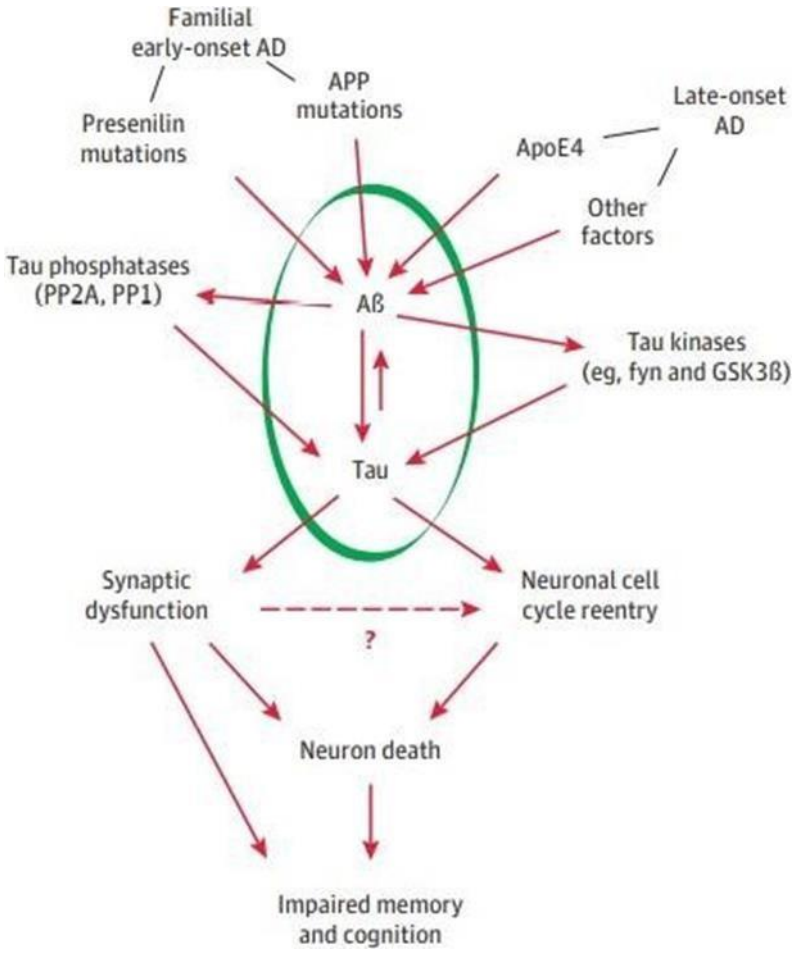

Figure 10: Alzheimer's disease (AD) development driven by beta-amyloid signaling via Tau (Bloom, 2014)

APP mutations, presenilin which causes familial early-onset AD also ApoE4 and other factors which causes late-onset AD promotes accumulation of toxic beta-amyloid plaque. Toxic

substances cause pathological tau development by regulating protein kinases as well as phosphatases that control tau phosphorylation and by causing tau misfolding. Tau toxicity is responsible for the synaptic malfunction and cell death that characterize memory and neurocognitive impairment in Alzheimer's disease, and as a result, tau is required for the characteristic harmful outcomes of beta-amyloid (Bloom, 2014).

Chapter 3

Current treatment options available for AD

3.1 Cholinergic Hypothesis

Since Alzheimer's develops, brain cells perish and links amongst cells are gone, producing cognitive signs to deteriorate. Although these treatments do not prevent the harm Alzheimer's produces to neuron, they might help reduce or stabilize signs for a partial period by hampering certain compounds involved in moving information within the nerve cells of our brain (U.S. Food and Drug Administration, n.d.). Notwithstanding all the concentrated exploration after a preemptive or disease-adjusting interposition on behalf of AD, the outcomes have been unsatisfactory, which departed the cholinesterase inhibitors (ChEIs) and the N-Methyl-D-Aspartate-receptor competitor as the solitary US FDA-permitted treatments (Cummings et al., n.d.). Seeing that AChE enzyme gives 2 core binding positions for drug collaboration, the catalytic position and the Peripheral Anionic Site (PAS), additional theory to be deliberated is the outcome regarding AChE enzyme into the amyloid peptide accumulation. This is recognized that AChE having an anionic obligatory position to perform a significant part in the procedure of amyloid accumulation, which might be another objective for AChE preventer that precisely attach to this position or might perform as multi-point groups, commanding to a diminish in the disorientated panel foundation (Belluti et al., 2005).

3.2 Donepezil

Donepezil hydrochloride is an acetylcholinesterase inhibitor very ordinarily expended for the healing of Alzheimer illness (Asiri & Mostafa, 2021). The first principle which was projected to describe AD known as the cholinergic hypothesis and has meanwhile directed to the improvement of the lone drugs presently permitted to handle minor to major AD (Bartus, 2000; Bartus et al., 1982). Damage regarding cholinergic neurons remains another deep-rooted

pathology of Alzheimer’s illness. Through late-stage Alzheimer’s illness, the amount regarding cholinergic neurons remains dramatically abridged; in several portions of the mind there is in excess of 75% damage (Bergmann et al., 1978). Cholinergic transmission is expected to be unfavorably vital for remembrance, learning, attentiveness and other advanced brain utilities. Cholinesterase inhibitors expand the obtainability of acetylcholine on synapses into the brain and remain one of the few medicine treatments that have verified to clinically suitable in the handling of AD dementia, thus authorizing the cholinergic method as a significant remedial aim in the illness (Hampel et al., 2018). Beneath standard circumstance Acetyl Co Enzyme A and choline in existence regarding choline acetyltransferase synthesize acetylcholine and while the neurotransmitter acetylcholine remains freed into the synapse, This impasses (triggers) postsynaptic receptor, consequently communicating a sign from a neuron to other (Arvanitakis et al., 2019). The enzymes acetyl cholinesterase (AChE) and/or butyrylcholinesterase (BChE) break down excess neurotransmitter in the synaptic cleft into cholinergic and acetyl, which would then be recycled into acetyl coenzyme A through a filtration (Hampel et al., 2018). Inhibitory neurotransmitters prevent the molecule acetylcholinesterase from dissolving the nerve cells into acetate and choline, increasing acetylcholine levels and persistence in the central nervous system (Akıncıoğlu & Gülçin, 2020). Tacrine was known as the very first medicine which was FDA-approved for the therapy of Alzheimer's disease in 1993, over than forty years after first being manufactured. Tacrine stands a centrally interim alterable cholinesterase inhibitor through extra pharmacological movement on monoamine stages, besides ion channels (Racchi et al., 2004). Tacrine & physostigmine, the very first ChE antagonists seemed to treating Alzheimer's disease, were linked to an increased rate regarding gastrointestinal (GI) adverse events (AEs) as well as other issues, especially hepatotoxicity (Jackson et al., 2004). In well-designed quick tests (Fourteen to Thirty weeks), donepezil Five and Ten mg/day drastically enhanced cognition and large - scale clinical feature compared

regarding placebo in 161 to 818 people with uncomplicated to moderate AD (Dooley & Lamb, 2000). Long period efficiency data propose that developments in understanding, worldwide function are preserved for nearby twenty-one to eighty-one weeks by donepezil (10 milligram per day in maximum patients) (Seltzer, 2007). Donepezil, a transitory and selective antagonist of acetylcholinesterase (AChE) derived upon piperidine, was indeed the 2nd ChE antagonist to gain FDA clearance for the clinical healing regarding minor to moderate Alzheimer Disease (Jackson et al., 2004). Pre - clinical research proposes that, in addition to acetylcholinesterase prevention, donepezil might have anti-AD modes of act (Seltzer, 2007).

3.3 Galantamine

Galantamine which actually known as a cholinesterase inhibitor that inhibits the degradation of acetylcholine neurotransmitter by binding towards the active center regarding the acetylcholinesterase in a reversible and selective manner (Raskind, 2003). Galantamine occurred beyond efficient than placebo regarding the improvement of the cognitive occasion (Loy & Schneider, 2004). Galantamine has now been considered to be an ideal allosteric modulation of nAChRs, causing modifications in the specific receptor particle that enhance its reactivity to Ach (Aarsland et al., 2003). The most effective dosage seems to be 16-24 mg per day, which is the permitted sustaining dose level in most areas (Razay & Wilcock, 2008).

3.4 Rivastigmine

Rivastigmine seems to be a non - competitive organophosphate cholinesterase inhibitor that is licensed for the cure of mild to moderate Alzheimer's sickness. It is a potent slow-reversible carbamate cholinesterase inhibitor. Rivastigmine has been proven to have favorable impacts in calculations of cognition and large input in randomised, twofold, placebo-measured tests lasting up to six months (Desai & Grossberg, 2005). Rivastigmine is approved for usage in sixty nations, along with all European Union member states and the United States, where it was

approved by the FDA since April 2000. Rivastigmine, taken orally at 6-12 mg per day or trans dermally at 9.5 mg per day, likely to help persons with mild-to-moderate Alzheimer's illness (Birks et al., 2009). Rivastigmine has been the sole CNS inhibitor that blocks both acetylcholinesterase and butyryl cholinesterase enzymes (Nguyen et al., 2021). Rivastigmine transdermal medication distribution organisms seem to deliver confidence for the supervision of numerous illnesses, because of the benefits that they suggest in relationship with oral dosing forms (Siafaka et al., 2020).

3.5 Memantine

As an authorized therapy for the cure of Alzheimer's disease, memantine is a non-competitive N- methyl-D-aspartate blocker presently in use (The Use of Memantine in Neuropsychiatric Disorders: An Overview – AACP, n.d.). The majority of exuberant neurotransmission inside the brain, which is beneficial for both learning and memory building, is mediated by NMDA receptors (Monaghan & Jane, 2009). Scientists believe that the person may produce an aberrant elevation of glutamate levels by blocking glutamate absorption or stimulating glutamate production from glia, according to their research (Belov Kirdajova et al., 2020). Extracellular calcium is released upon glutamate attachment towards the NMDA receptor, which is responsible for controlling membrane responsiveness and neurotransmission (Carvajal et al., 2016). While glutamate contents become unusually increased, excessive activation of N-methyl-D-aspartate receptors will occur, which will result in an immoderate flow of calcium and eventually cell breakage, which would end in cell death (Belov Kirdajova et al., 2020). Memantine inhibits the activity of the N-methyl-D-aspartate receptor, hence limiting calcium entry into the brain cell (Olivares et al., 2012). When memantine is used alone it showed enhanced cognition, personality, tasks of daily life, general performance, and phase of impairment in Alzheimer's disease patients, and also it was nicely accepted by them. Furthermore, the impact size in respect of successfully executing was minimal, and as a result,

there is little indication that the treatment is providing therapeutic efficacy (Matsunaga et al., 2015). Researchers of meta-analyses showed that memantine, singly or in addition to ChEIs, can treat Alzheimer's disease in a way that is both effective and safe (Kishi et al., 2017). As per the findings, Memantine alone or in conjunction with such a cholinesterase inhibitor improves the prospects of people with a high risk of developing Alzheimer's disease much more than a placebo (Tariot et al., 2004).

3.6 Memantine+donepezil

There was no evidence of significant variability in the effectiveness of donepezil or memantine whether used in conjunction with or without the other medicine. Subgroup studies, on the other hand, failed to demonstrate any statistically significant advantages of combining memantine with donepezil medication (Howard et al., 2012). However, there was just a tiny variation in the recovery of brain performance in between the two therapies. The blending of memantine with a cholinesterase inhibitor was shown to be effective in cholinesterase inhibitor monotherapy in improving behavioral abnormalities (Matsunaga et al., 2015). Nevertheless, as matched to whichever memantine itself or control, the mixture of memantine with donepezil demonstrated greater benefits on behavioral and neuropsychological problems, the overall evaluation, and everyday routines (Guo et al., 2020).

3.7 Aducanumab

Aducanumab, an intravenously infused medication for treating Alzheimer's disease, has been authorized by the FDA which helps to remove beta-amyloid plaque (U.S. Food and Drug Administration, n.d.). Throughout a 54-week duration, aducanumab reaches the brain cell and reduces the beta-amyloid cluster in people having Alzheimer's disease. It is clear that aducanumab reduced amyloid deposits inside the brain regarding the patients with a history of proof of a high amyloid screening since the amyloid decline was dependent on the amount of

the drug (Vaillancourt, 2016). Amyloid plaque and hydrophilic oligomers are targeted by the human- specific antibodies, aducanumab. At the beginning of the study, 165 candidates having initial- stage Alzheimer's disease were given high infusions of 1, 3, 6, or 10 mg/kg each month. The results indicated substantial declines in the amyloid cluster in a dose-and-time-reliant way, with almost half of the candidates who obtained the 10 mg/kg amount no longer encouraging significant amyloid positron emission tomography afterward 12 months of treatment. Plaques appeared considerably reduced throughout all cortical areas of the brain that were studied (Schneider, 2020). Therapy must be begun in candidates having moderate cognitive decline, as per the prescription advice provided by the US Food and Drug Administration. This is the group wherein the medication was started in medical studies (Dhillon, 2021).

Chapter 4

Marine compounds to treat Alzheimer's disease

4.1 Bryostatin-1

4.1.1 Source

Products derived from nature Pettit and colleagues identified bryostatin-1 in *Bugula neritina*, a marine bryozoan, and bryostatin-1 is one of several macrocyclic lactones they discovered (Pettit et al., 1982). Marine bryozoans are a phylum of underwater invertebrate species that look similar to corals and may be found in a variety of settings, including salty and freshwater environments. Colonies of *Bugula neritina* are often seen in wharves and bays, offshore to a depth of 5 meters, adhering to any hard surface that is accessible. A number of studies have indicated that *B. neritina* larvae like to attach themselves to rough surfaces and to organic matter. Algae and well-established bryozoan colonies are only two examples of where they typically attach themselves. Water salinity ranges from 30 to 18%, making *B. neritina* a common sight in both euhaline and polyhaline environments.

4.1.2 Chemical structure

As a macrolide with an unusual polyacetate backbone, bryostatin-1 has been studied extensively in relation to the bryostatin family (Keck et al., 2011). Formula of bryostatin-1 is C47H68O17 (Pettit et al., 1982).

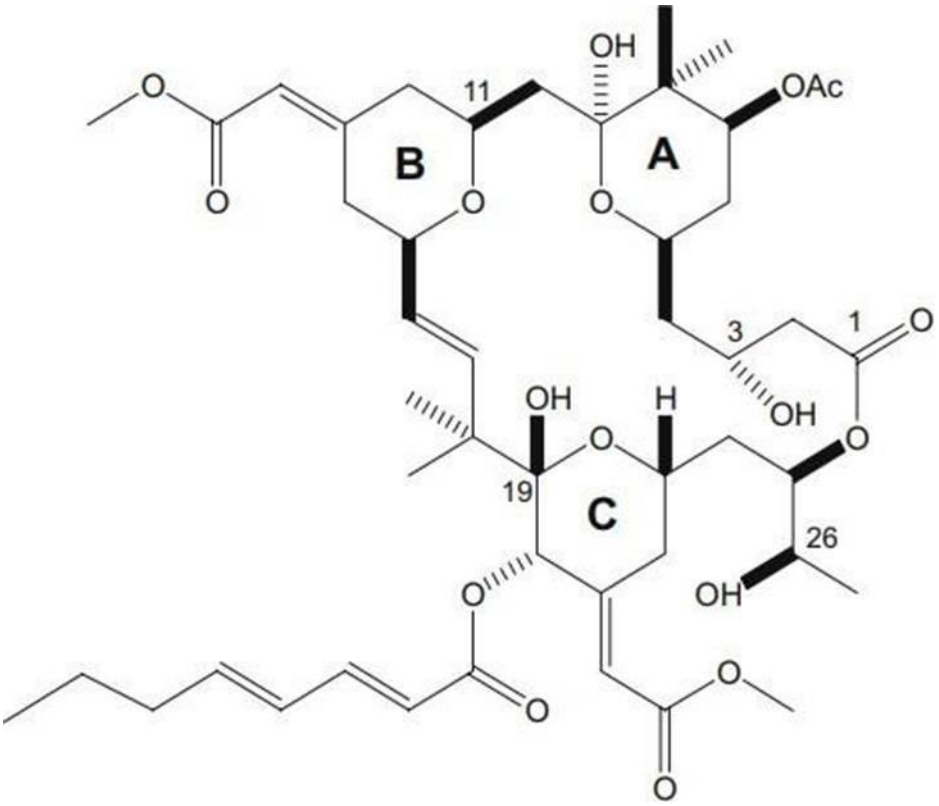

Figure 11: Chemical structure of Bryostatin-1(Hongpaisan et al., 2011)

4.1.3 Mechanism of action

The mechanism of action of bryostatin 1 in the central nervous system remains to be fully elucidated. However, its neuroprotective properties have been largely attributed to modulation of the protein kinase-C (PKC) enzyme. PKCs are serine-threonine kinases that dictate numerous cellular pathways, including growth, differentiation, apoptosis, and neurotransmission. Bryostatin 1 modulates the conventional (cPKC) and novel (nPKC) PKC subtypes by binding to their regulatory C1 domains (C1a and C1b). This interaction mimics the actions of their endogenous activator diacylglycerol (DAG), which is transiently produced in the inner leaflet of the plasma membrane in response to activation of numerous receptors. Upon its generation, DAG inserts into the DAG/phorbol ester-binding cleft of the C1 domains of the c/nPKCs, anchoring them at the plasma membrane and driving the conformational

change of the PKCs, leading to their enzymatic activation (Blanco et al., 2019). Activation of PKC, phosphorylation of the kinase, and transportation of PKC towards the cell surface are all facilitated by the attachment of bryostatin-1 with PKC. When PKC activates it enhances synthesis and production of BDNF which is a neuronal growth factor linked with cognitive performance in the CNS (Sun et al., 2015). Beta-amyloid has been shown to suppress PKC function, at partly, in patients with Alzheimer's disease. Proteins required and adequate for the following great memory formation are newly generated as a result of stimulation of PKC by bryostatin-1.

4.1.4 Preclinical and clinical evidences

Tg2576 AD mouse models aged 5-6 months were treated with stimulator bryostatin to prevent cell damage and lowering of PKCε activity (Sen et al., 2018). When PKCε is depressed, brain-derived neurotrophic factor (BDNF) levels are decreased leading to neuronal damage. According to preclinical studies, intravenous bryostatin 1 treatment in AD mutant mice models stimulates PKCε inside the brain and inhibits beta-amyloid buildup, loss of synapse, and memory deficiency (Etcheberrigaray et al., 2004; Hongpaisan et al., 2011). Bryostatin-1 has also been shown to directly boost cognitive performance in experimental rats at adequate dosages. According to the research, oral bryostatin treatment improves learning and memory in an alzheimer's disease animal model (Schrott et al., 2015). Alpha-secretase activation is likely mediated by PKC in the presence of Bryostatin-1 because under bryostatin-1 administration, it activates non-amyloidogenic route of amyloid precursor protein. When PKC is activated on APP mouse models, beta-amyloid 40 levels inside the brain are reduced. Bryostatin was shown to improve the Mini-Mental State Examination (MMSE) results of six Alzheimer's disease patients compared to three placebo-treated patients in a Phase IIa clinical investigation. There were no major side effects linked with bryostatin within those patients with Alzheimer's disease. Over 60 minutes of injection, PKCε quantities in peripheral blood

mononuclear cells found to be significantly higher, as well as blood bryostatin concentrations. When bryostatin was used for a long period of time and at high doses (25 μg/m2), PKCε downregulation occurred when supplied for five or six weeks in a row. Bryostatin was also shown to be a promising medication candidate in the treatment of Alzheimer's disease in this investigation (Nelson et al., 2017). Three extremely symptomatic individuals with Alzheimer's disease got numerous bryostatin injections over the course of 5 to 9 months in an extended access study. The authors report fast and long-lasting changes in behavior following the first treatment (Bryostatin 1 | ALZFORUM, n.d.). Bryostatin enhanced effectiveness, acceptability, and tolerability while provided to 150 individuals with advanced Alzheimer's disease to improve cognitive performance, seen in a phase 2 medical trial. The whole analysis set yielded no meaningful primary endpoints, which is unusual. It was found that the group having 20μg bryostatin showed positive result compare to the control group in statistical analysis. Though according to the data, bryostatin 20μg therapy for Alzheimer's disease needs more clinical testing in case of its efficacy (Kabir et al., 2021). Twenty percent of the participants in both the 20μg and control subjects discontinued the study due to adverse effects. There were double quite so many dropouts in the 40μg treatment and greater harmful impacts. Both doses were ineffective in the entire trial population (Farlow et al., 2019). The simultaneous integrated-boost for the 20μg dosage increased when the researchers only looked at individuals who finished the whole treatment schedule. According to the results of an exploratory study, the improvement was only seen in those who were not getting memantine (Bryostatin 1 | ALZFORUM, n.d.). June 2018 saw the beginning of another phase II investigation for 108 people with Alzheimer's disease who did not take memantine. Patients were separated into two parts based on the MMSE values, 10–15 vs 4–9, in that research study. Such divisions were then randomly assigned to receive whichever 20μg bryostatin or placebo. Over the course of twelve weeks, a total of seven dosages were provided but no positive findings were seen in the

investigation (A Study of Bryostatin in Moderately Severe to Severe Alzheimer's Disease Subjects Not On Memantine - Full Text View - ClinicalTrials.Gov, n.d.). A third Phase 2 experiment with individuals with sensible dementia caused by Alzheimer's disease who aren't really receiving memantine began in August 2020 and will conclude in November 2022 (Bryostatin 1 | ALZFORUM, n.d.).

4.2 Homotaurine (Tramiprosate)

4.2.1 Source

Especially when it comes to mediterranean red algae (*Hypnea boergeseniid, Gracilaria corticate, Gracilaria pygmaea),* homotaurine, a tiny aminosulfonate molecule that is found throughout the algae also it can be found from green algae (*Caulerpa racemosa, Cladophora densa*), brown algae (*Cystoseira indica, Cystoseira trinodis),* unicellular green algae (*Ostreococcus, Micromonas*). It has really been demonstrated to have a significant neuroprotective impact due to its unique anti-amyloid action and its affinity for the gamma aminobutyric acid class A receptor.

4.2.2 Chemical structure

Unlike taurine, homotaurine molecule contains an extra carbon inside its chain. The selectivity for GABA receptors of this chemical makes it a controller of hyperactive neurotransmission. Its chemical formula is C3H9NO3S.

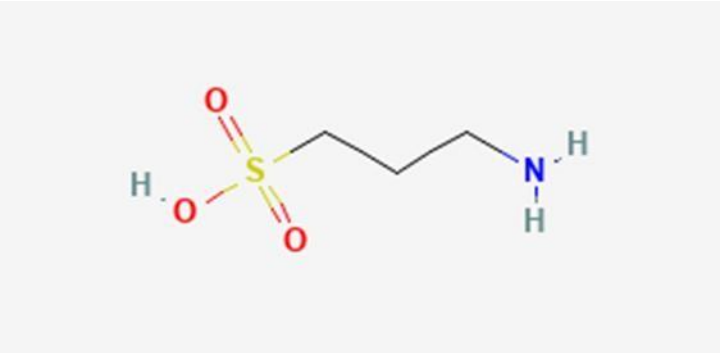

Figure 12: Chemical structure of Homotaurine. National Center for Biotechnology nformation (2022)

4.2.3 Mechanism of action

Tramiprosate has been shown to inhibit the misfolding of beta amyloid oligomers by covering the amyloid peptide with a protective layer. This disease's beta-amyloid oligomers are thought to be the main culprit. When misfolded proteins are prevented from assembling into amyloid oligomers by the homotaurine mechanism, amyloid aggregation, which causes neurodegeneration and the clinical development of Alzheimer's disease, does not occur. A sample of AD patients with a genetically determined subtype was studied in homotaurine investigations following phase III clinical trials of tramiprosate in AD patients yielded this genetic information (M. Silva et al., 2021).

4.2.4 Preclinical and clinical evidences

Tramiprosate has been shown in preclinical tests to reduce beta-amyloid oligomer production and the accumulation of amyloid plaques in a mouse model of AD. This drug lowered the levels of amyloid proteins which are soluble and as a result reduced the formation of amyloid plaques inside the brain (Gervais et al., 2007). In a critical Phase 3 clinical trial, homotaurine's therapeutic effectiveness in AD was studied, however the desired outcome was not met. There

was a substantial reduction in hippocampal fluid loss and a slower downturn in cognitive performance in the overall group as well as a slight decrease in global mental impairment in specific gene carriers of the APOE4 gene that was seen in post-hoc assessments, proposing that homotaurine may have disease-modifying consequences (Caltagirone et al., 2012; Tsolaki, 2019). Tramiprosate administration in TgCRND8 mice resulted in a considerable decline like almost 30 percent within the brain beta amyloid burden and a massive drop like 20–30 percent within cerebral contents of soluble as well as insoluble beta-amyloid 40 and 42 (Gervais et al., 2007). Tramiprosate reduced beta-amyloid plasma concentration in such a dose-dependent way, which shows that tramiprosate contributes to brain beta-amyloid conversion or distribution (Tanvir Kabir et al., 2021). Furthermore, tramiprosate had no effect on tau's binding to microtubules; rather, it facilitated the decrease of potentially hazardous tau-actin compounds. Tramiprosate inhibits amyloid accumulation inside the brain by binding to the soluble amyloid. Preclinical as well as clinical investigations using this medication showed improvements in oligomeric as well as fibrillar amyloid plaque, hippocampus atrophy and also in cholinergic transmission. It also improved mental stability (Manzano et al., 2020). On preliminary findings from the volumetric MRI cohort, tramiprosate appears to delay hippocampus shrinkage and improve cognition (Gauthier et al., 2009). A strong correlation between tramiprosate dosage and decreased hippocampus compaction levels was found. Patients having mild-to-moderate Alzheimer's disease were treated with tramiprosate in such a phase 2 clinical trial, and the results showed that tramiprosate reduced beta-amyloid 42 levels in their CSF without harming them. These findings in CSF as well as widely prescribed data imply that tramiprosate has a function in illness modulation. Tramiprosate was also shown to be well enough and harmless following a three-month therapy (Kabir et al., 2021). Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) showed a favorable trend in patients receiving 150 mg twice daily in two different phases III studies, which included 2025 individuals with

moderately severe AD with the ApoE4 allele distribution. It's interesting to note that patients without APOE4 showed no therapeutic advantages, but those with APOE4 showed an intermediate degree of effectiveness (Abushakra et al., 2017). Tramiprosate was administered to 1703 people, including 288 healthy people, 24 people with amyloid angiopathy including 1391 people with Alzheimer's disease. Homotaurine was found to be harmless and quite well in each of these investigations when taken at the prescribed dose of homotaurine 100mg two times a day. 58 AD patients having mild symptoms have been randomly allocated to take placebo or tramiprosate at doses of 50mg, 100mg, 150mg for three months in a controlled, double-blind, placebo-controlled Phase II research (Aisen et al., 2008). The most common discomfort effects included dizziness, vomiting tendency, also diarrhea, that were relatively mild in intensity and did not cause any significant adverse effects. During a three-month trial, tramiprosate was shown to pass the blood-brain barrier as well as lower beta-amyloid 42 contents in the CSF of Alzheimer's disease patients, showing that it may be used to treat the illness's underlying pathology and alter its progression (Caltagirone et al., 2012).

4.3 Dictyostatin

4.3.1 Source

Dictyostatin was first found by Pettit and other scientists at Arizona State University in 1994 from the marine sponge of the genus *Spongia sp*. which was found in the Republic of Maldives (Florence et al., 2008), whereas Wright and coworkers isolated it from *Corallistidae sp.* of the North Jamaican coast.

4.3.2 Chemical structure

The molecular formula of 22-membered Macrolacton dictyostatin is C35H52O6.

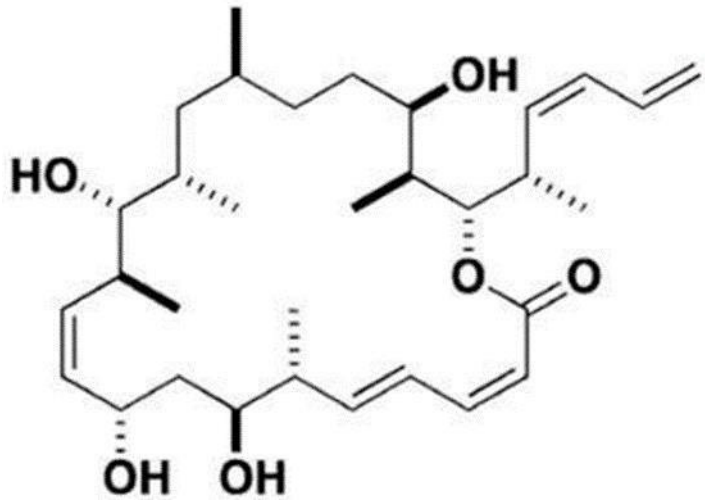

Figure 13: Chemical structure of Dictyostatin (Dombrowsky et al., n.d.)

4.3.3 Mechanism of action

The most effective microtubule stabilizer is dictyostatin. Dictyostatin enhances microtubule stability by engaging with beta-tubulin. The G(2)/M stage of the cell cycle was shown to be blocked by dictyostatin-1 in initial experiments. When these cells were stained with anti-tubulin, it was discovered that they had several aster forms as well as microtubule matrix bundlings. In vitro, dictyostatin-1 was able to promote polymerization of tubulin, and the polymerized tubulin remained stable even at low temperatures. According to a report in case of mice it crossed the blood-brain-barrier and extended the stabilization of microtubule. (Ballatore et al., 2012). So basically, what happens is microtubule becomes stabilized so no insoluble filaments are formed. It amplifies microtubule rigidity and reduces axonal dystrophy, associated with lower levels of tau pathology, as well as a potential to increase the rate of survival of hippocampus neurons in animal models of Alzheimer's disease.

4.3.4 Preclinical and clinical evidences

Tau has been shown to be abnormally hyperphosphorylated in Alzheimer's disease (AD) (Whittington et al., 2013). Inside a PS19 tau Tg transgenic mice, Makani et al. assessed the effectiveness of dictyostatin. Lower microtubule density and axonal dystrophy were detected in PS19 transgenic mice which were given distyostatin compared to vehicle-treated PS19 transgenic mice, coupled with reduced expression of tau pathology as well as a propensity forward with an enhanced survival rate of hippocampus cells (Kabir et al., 2021). Molecules that stabilize microtubules may be useful in the treatment of Alzheimer's disease (Ballatore et al., 2012). Beta-Amyloid oligomers as well as neuronal injury are the two most important causes of Alzheimer's disease that must be addressed. Dictyostatin has antiamyloidogenic characteristics as well as the ability to pass the blood-brain barrier more effectively. APP/PS1 AD mouse aged 15- 16 months were treated with dictyostatin under a variety of therapeutic interventions and found to regain the memory without even any decline in plaque. According to a recent study, Dictyostatin is a promising medicine for treating Alzheimer's disease (AD) (Balducci et al., 2018). A trial of 101 people having MCI found that doxycycline caused a significant decline in SADAS-cog with time versus placebo (Molloy et al., 2013).

4.4 Docosahexanoic Acid (DHA)

4.4.1 Source

Since the late 19th century, researchers have investigated chloroplastless heterotrophic mediterranean microalga for example *Schizochytrium mangrovei, Schizochytrium limacinum, Thraustochytrium aureum* and discovered that it is an excellent source of DHA, which is essential for the development and the functioning of the neurological system (De Swaaf, 2003; Ma et al., 2007). Inadequate DHA levels are linked to a variety of AD symptoms, whereas regular or higher DHA levels can prevent or ameliorate these symptoms (Ma et al., 2007). Even

while omega-3 fatty acids derived from plant may be used to produce DHA, this metabolic route is unsuccessful in humans. Marine diets and supplementation are the primary sources of DHA for human brain (Adarme-Vega et al., 2012). A crucial fatty acid in sustaining healthy brain function as well as the development of cognitive abilities, docosahexaenoic acid is an essential nutrient. Many neurodegenerative diseases are caused by DHA deficiency, hence dietary supplementation is necessary to preserve cognitive function (Balakrishnan et al., 2021).

4.4.2 Chemical structure

Commercially produced from microalgae, DHA is a 22-carbon chain having six cis double bonds that have anti-inflammatory properties. Molecular formula of DHA is C22H32O2. (Calder, 2010).

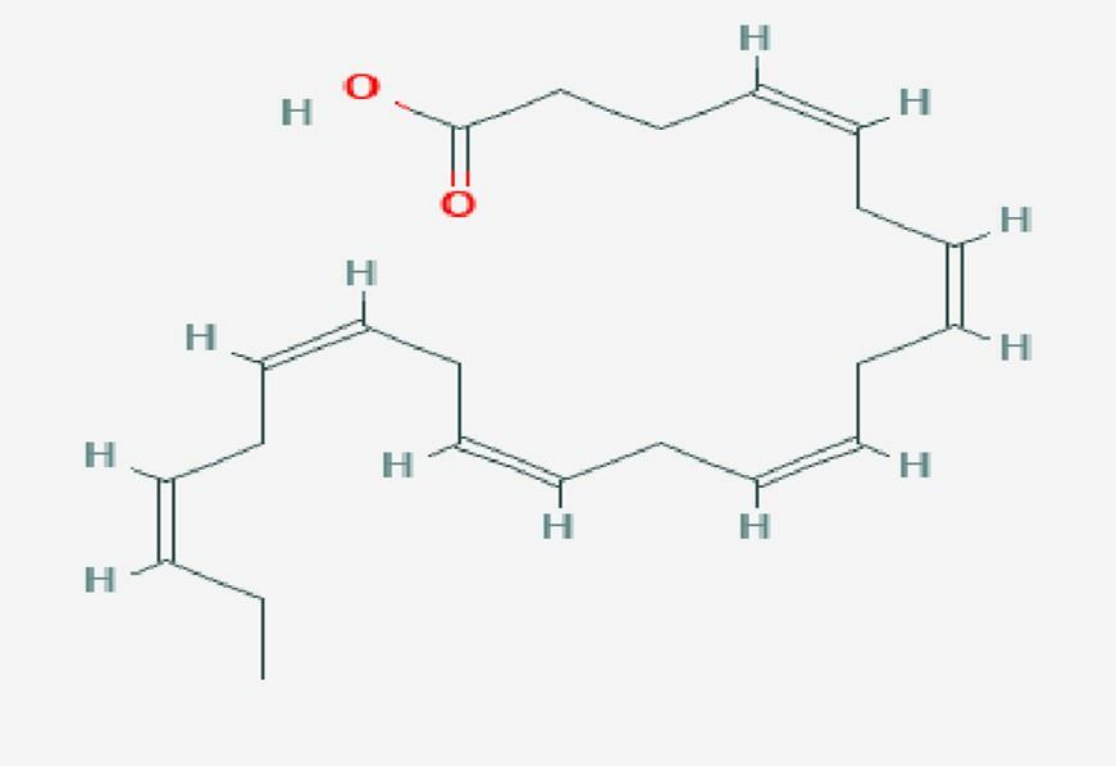

Figure 14: Structure of DHA (Calder, 2010)

4.4.3 Mechanism of action

It's possible that DHA has a direct impact on amyloid-beta in the experiment or in vivo and that can diminish tau intraneuronal development. Deficiency in DHA can disrupt the activity of membrane-bound enzymes as well as trans-membrane transport capacities, impacting neural transmission and learning capacity. DHA is also essential for membrane fluidity. Cell's future signaling is influenced by DHA, which promotes neuronal survival and proliferation in the hippocampus, which is lost as a result of Alzheimer's disease (AD) (Cerebral Circulation: Definition and Patient Education, n.d.) (Heath & Wood, 2021)

4.4.4 Preclinical and clinical evidences

Patients with mild to severe dementia and Alzheimer's disease benefitted from DHA supplementation because it reduced the accumulation of beta-amyloid plaque, related toxicity and the formation of beta-amyloid plaque as well as an increase in beta-amyloid plaque clearance (Grimm et al., 2013; Sharman et al., 2019). Tau tangles were also decreased as a result of DHA supplementation. DHA supplementation decreased tau pathology in animals, according to research (Cole & Frautschy, 2010; Patrick, 2019). As per Freund-Levi, a small number of individuals with mild Alzheimer's disease were found to be benefited with DHA treatment according to a study (Freund-Levi et al., 2006). Due to the fact that DHA is an essential component of all cell membranes, it modulates glucose supply to the brain through modulating GLUT1 transporters (Patrick, 2019). DHA deprivation lowered GLUT1 transporters in case of rat models by up to 30%, but supplementation using DHA increased GLUT1 transporters significantly 37% and increased glucose uptake by endothelial cells (A. X. Da Silva et al., 2002; Pifferi et al., 2007). Phosphorylated tau protein with in the CSF regarding Alzheimer's disease patients was shown to be lower after taking around 2 grams of DHA supplementation daily for six months (Fraga et al., 2017; Freund Levi et al., 2014). As

per a study, a number of 854 individuals were initially screened, and 86 individuals ended up meeting the study's requirements and were randomly assigned to receive either omega-3 polysaturated fatty acid (PUFA) (44 individuals) or a placebo (42 individuals). The results revealed that participants in the experimental group experienced greater improvements than those in the placebo group in terms of cognitive features like conceptual thinking, space visuals effectiveness and cognitive ability (Bo et al., 2017). As part of a North American AD Cooperative Research, DHA therapy was given to 402 people having mild-to- moderate Alzheimer's disease for almost 18 months; 295 people completed the study. DHA seemed to have no effect on the rate of deterioration when compared to a placebo. ApoE4 noncarriers were shown to have a lower cognitive impairment than ApoE4 carriers, who may have had a more advanced form of Alzheimer's disease (Kabir et al., 2021).

4.5 Rifampicin

4.5.1 Source

As an antibiotic, rifamycin is obtained from *Amycolatopsis rifamycinica*, although it may also be produced by marine bacteria—*Salinispora* which is isolated from the marine sponge *Pseudoceratina clavate* (Chromy et al., 2012; SINGH, 2013). Rifampicin has shown significant neuroprotective action in multiple studies, in contrast to its usual anti-infectious effect.

4.5.2 Chemical structure

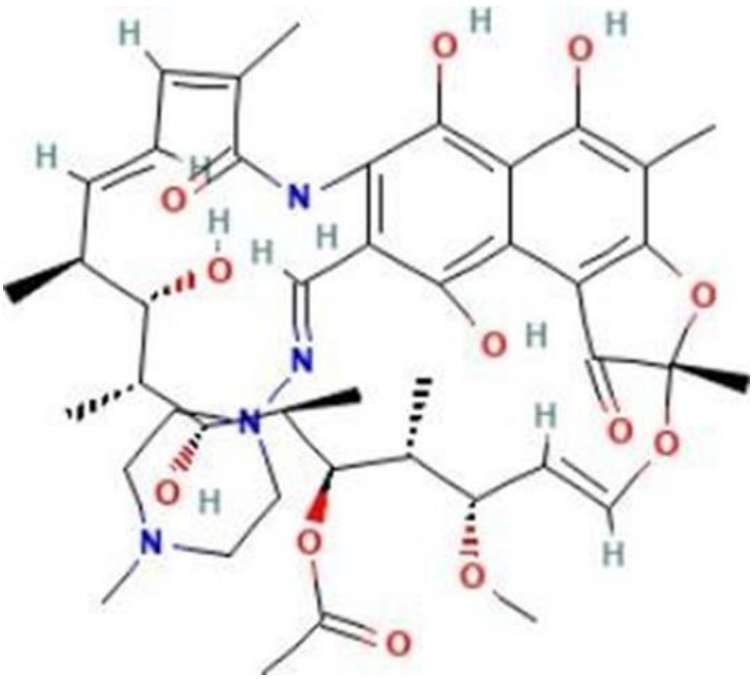

Figure 15: Chemical structure of Rifampicin. National Center for Biotechnology Information (2022)

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4.5.3 Mechanism of action

Free radical damage as well as neuroinflammation both are reduced by rifampicin, thereby enhance neuroprotective effects (Bi et al., 2011; Yulug et al., 2018). Beta-amyloid formation is aided greatly by the production of free radicals. Compared to vitamins, rifampicin suppressed beta- amyloid aggregation 10 to 100 times better. In order to pass the blood-brain barrier, Rifampicin is composed of a naphtho-hydroquinone-chromophore bridging with the help of a lipophilic ansa- chain which is solely accountable for drug transport (Tomiyama et al., 1997). The ansa-chain of rifampicin is not necessary to reduce beta-amyloid agglomeration, according to separate research, but the lipophilicity of rifampicin plays a vital role in case of supplying the drug inside the brain. So basically, it relieves inflammation of the brain and protects it from free radical damage; inhibits fibril production and also beta-amyloid aggregation.

4.5.4 Preclinical and clinical evidences

This drug's anti-amyloid efficacy has been demonstrated by several in vitro investigations, along with the inhibition of fibril development and toxicity by the amyloid peptides which has been aggregated before (Tomiyama et al., 1997). According to Mark B. Loeb's research, 300mg of rifampin given for three months can help people having mild- to-moderate Alzheimer's disease (Loeb et al., 2004). According to a study, Rifampicin has been demonstrated to have a significant impact on the accumulation of tau oligomers as well as beta- amyloid plaque in transgenic animal models. Amyloid-oligomer buildup, hyperphosphorylation of tau, loss of synapse and activation of microglia were reduced in 13-month-old Tg2576 mice given rifampicin orally at dose of 0.5mg every day for one month. Tau oligomer buildup, hyperphosphorylation of tau, loss of synapse, and activation of microglia were all decreased in a dose-dependent manner by rifampicin therapy given in 14-15-month-old tau609 mice at dose of 0.5 and 1 mg every day for one month, and memory was improved nearly entirely when given at 1 mg per day (Umeda et al., 2018). Memory impairments were reduced in AlCl3 rats treated with rifampicin, as well as better histopathological changes and locomotor performance as compared to AlCl3 rats not given the drug (Kaur & Sodhi, 2015). T.lizuka performed a research that found that rifampicin's preventative impact depends on the dosage and the length of therapy, and also that the impact requires minimum 450mg once in a day for almost one year. Fluorodeoxyglucose-uptake inside the Posterior Cingulate Gyrus (PCG) was markedly improved by rifampicin therapy at a dosage of 450 mg per day for almost one year, that was also evident mostly in MMSE ratings (Iizuka & Kameyama, 2017). Model mice for Alzheimer's disease showed improved cognition and decreased neuropathology when rifampicin was administered subcutaneously or sprayed into the nostrils. The maximum rifampicin brain delivery was observed with intranasal administration (Umeda et al., 2018).

Intranasal injection of rifampicin is the most convenient and least intrusive method for long-term dosage. Neurofibrillary tangles (NFTs) as well as senile plaques (SPs) were found inside the brains of 16 leprosy patients with no dementia in a study of 140 elderly Japanese volunteers. Leprosy sufferers who were treated with rifampicin had an abnormally low prevalence of senile plaques within their brain compared to age-matched peers (Namba et al., 1992). Rifampicin oral dosing of 300 mg per day over three months resulted in a substantial improvement in cognitive performance in 101 individuals having mild-to-moderate Alzheimer's disease (Loeb et al., 2004).

4.6 Gracilins

4.6.1 Source

Marine sponges produce a class of diterpenoids known as gracilins. In 1985 Gracilin was discovered and extracted from the mediterranean sponge *Spongionella gracilis* which was the very first analog to be structurally characterized (Mayol et al., 1985).

4.6.2 Mechanism of action

All analogs, except for Gracilin A, were shown to have the strongest immunosuppressive as well as neuroprotective effects. The diacetoxyhexahydrodifuro group is present in all of the analogs. Extracellular signals can control the kinase enzyme beta-secretase 1, which these drugs can block (M. Silva et al., 2021). As a result, tau protein hyperphosphorylation is reduced. Gracilins protect neurons and fight free radicals by activating Nrf2 and concentrating on mitochondria (M. Leirós et al., 2015). Gracilins protect primary neurons from damage by restoring mitochondrial functions and preventing the conventional uncoupling of oxidative phosphorylation from causing changes (Marta Leirós et al., 2014). Amyloid—induced reactive oxygen species (ROS) generation is reduced by gracilins' capacity to suppress the

phospholipase A2 enzyme which inhibits the enzyme's ability to produce ROS (Gegunde et al., 2019). The impairment of mitochondrial function and, by extension, neurodegenerative disorders are linked by oxidative damage. Gracilins' potential for neuroprotection raises the possibility that they might be promising first-in-class anti-AD medication options. Synthetic gracilin A derivatives with high neuroprotective effects were made using a pharmacophore-directed organic synthesis technique.

4.6.3 Preclinical evidences

A research demonstrated how gracilin A analogues protected SH-SY5Y cells from hydrogen peroxide-related harm which ultimately helps in reducing ROS levels, enhancing matrix metalloproteinase (MMP), and increasing cell survival (Alvariño et al., 2019). These findings suggest that gracilins given at 0.4 mg per kg may improve cognition, therefore expanding the number of animals in each group or lengthening the duration of therapy may improve the behavioral outcomes seen here while also reducing Aβ buildup in vivo. Extracellular Regulated Kinase (ERK) is inhibited by gracilin molecules, which also lower tau phosphorylation at Ser202 as well as Thr205 (Leirós et al., 2015). Gracilin A analogues have recently been shown to have neuroprotective characteristics, making them attractive therapeutic candidates for Alzheimer's disease. It was found that the derivatives 2 as well as 3 had the most promising criteria to be a lead compound in case of further drug development (Alvariño et al., 2019).

Chapter 5

Conclusion

For cuing human Alzheimer's disease, oral Bryostatin-1 is a unique, effective, and long-acting cognitive booster. Oral Bryostatin-1 dramatically enhanced memory, especially in the first three days of testing (Schrott et al., 2015). To enhance memory in people with cognitive impairment, homotaurine supplementation has anti-inflammatory characteristics. Homotaurine's beneficial disease-modifying effects have been maintained, encouraging further confirmation studies for curing genetically defined communities with moderate Alzheimer's disease and uplifting future studies into the processes under which this substance might regulate brain inflammation even during the progression of degenerative brain dementias (Bossu et al., 2018). Alzheimer's disease (AD) patients in the initial stages may benefit from tramiprosate effects on the degeneration of neurons, irritation, and hippocampal shrinkage. Identifying subcategories of highly responsive individuals and the biological and clinical markers of response will also be a key problem. Disease-modifying and symptomatic therapy are the most pressing issues in the treatment of neurocognitive disorders today. There have been encouraging outcomes in this area with all of these marine-derived chemicals (Manzano et al., 2020). Further clinical trials need to be conducted for marine compounds to be used in alzheimer’s patient. Along with that combination therapy consisting of marine compounds have a prospect of displaying better activity that need to be tested.

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