A BRIEF REVIEW ON ALZHEIMER’S DISEASE

1.1 Reviews on Alzheimer’s disease.

Alzheimer’s disease (AD) is a neurodegenerative disorder progressive of the brain that causes problems with memory, thinking, and behavior. In the year 1901 Nov 25, Dr. Aloysius Alzheimer, a German Neuropathologist and psychiatrist, first observed in one of his patient (Auguste deter) (shown in Fig. 1.1.1) 51-year-old women had weird behavioral symptoms with a loss of short-term memory, confusion, disorientation, auditory hallucinations, pronounced psychosocial impairment, trouble in expressing her thoughts and unfounded suspicions about her family and hospital staff [1].

Fig. 1.1.1. Dr. Alois Alzheimer’s and patient Auguste deter in 1902.

On 8 April 1906, Auguste Deter died; Alzheimer had made a deal to receive her medical records and brain to Munich where he was working in Kraepelin's laboratory. With two Italian physicians, he used the staining techniques of Bielschowsky to identify amyloid plaques and neurofibrillary tangles. These two microscopic deposits that have become hallmarks of the disease. Subsequently, Alzheimer described second case, that of Johann F., whose brain differed in that it lacked NFT- a “plaque-only” case. Such case remains part of the modern disease type [2]. These two initial cases, (Auguste D and Johann F) published as “Persenile dementia” by Alzheimer, later became labeled...
Alzheimer’s disease by Kraepelin [2]. Incredibly, histological slides of both cases have survived to the present and modern re-examinations confirm Alzheimer’s original findings [2].

Today; Alzheimer’s is at the facade position of biomedical research with 90% discovered in the last 15 years. A few of the most notable progress has shed light on how Alzheimer’s disease affects the brain. Alzheimer’s disease is the most general form of dementia in the elder persons. This state is characterized by a progressive deterioration of virtual loss of memory, cerebral functions, augmented laziness, decreased speech function, and disorientation. It is also one of the best recognized and important of all neurodegenerative disorder. Alzheimer’s disease is a disease that is caused by or as a result of diminished metabolic activity in the brain [3]. It is a state that is connected with considerable psychological and emotional distress for patients and their family members. It also symbolizes a large financial burden for those affected and their families because of the long-term care that is related to the condition. The disease is caused by altered in the basal forebrain, cerebral cortex and other areas of the brain. The peak frequency of the early development of Alzheimer’s disease is in individuals between the ages of 65 and 74 years. It is projected that 3.5% of the population in the United States between the ages of 65 and 74 years of age is in at least the initial stage of Alzheimer’s disease. Mainly individuals who have an advanced disease are 85 years of older age. Females are little more likely than males to develop Alzheimer’s disease.

**Risk factors**

While researchers know that Alzheimer’s disease involves the breakdown of nerve cells, why this happens is still unidentified. However, they have identified certain risk factors
that increase the possibility of developing Alzheimer’s. Numerous endogenous and exogenous Alzheimer’s disease risk factors have been recognized, herein termed Alzheimer’s risk factors (ARF). Various factors undoubtedly work synergistically and additively to increase Alzheimer’s disease risk.

Risk factors are two types;

Non-modifiable risk factors and modifiable risk factors.

**Non-modifiable Alzheimer’s risk factors**

(i) **Age**

Aging is a greatest known risk factor for Alzheimer’s disease. Most of the persons with the Alzheimer’s are 65 and older. The probability of developing Alzheimer’s approximately two times every five years after age 65. After age 85, the risk attains nearly 50%. An entropic (increasing disorder) analysis of Alzheimer’s disease, precisely pointing to advancing age as the most significant risk factor for the disease and hypothesizing aging alone could account for its causation [4]. Argument of Drachman against seeking a single pathophysiological factor (e.g., amyloid accumulation), but rather suggested effective Alzheimer’s disease prevention might instead depend on recognition of contributions from a multiplicity of age related changes and reducing their burden as much as possible.

(ii) **Family history and genetic susceptibility**

Research has revealed that those who have a parent, brother or sister with Alzheimer’s are two to three times more probable to develop the disease. The risk increases if more than one family member has the Alzheimer’s disease. Although late-onset Alzheimer’s disease, the most common form of the disease, has relatively minor heritability [5].
(iii) Down syndrome

Down syndrome is firmly established as extremely genetic and major risk factor for AD. Down syndrome is a developmental disorder caused by inheritance of an additional copy of chromosome 21, although the etiological relationship between the chromosome 21 genes and the Down syndrome pheno-type is multifaceted [6]. A gene that encodes for amyloid precursor protein (APP) resides on chromosome 21. It is thought on Down syndrome the extra copy of the amyloid precursor protein gene once activated can cause abnormalities in the processing of amyloid and its subsequent deposition in plaque. Other than in Down syndrome, inherited alteration of this gene causes an autosomal dominant form of Alzheimer’s disease [7].

(iv) Traumatic brain injury (TBI)

All major head injuries, including concussions, can considerably increase the risk of Alzheimer’s disease. Within a few hours following TBI, abnormal patterns of amyloid and tau deposition appear in injured brain tissue [8]. Frequent mild Traumatic brain injury accelerates amyloid deposition and rates cognitive impairment. Sports such as boxing, ice hockey, soccer and football facilitate head injuries. Boxers who have had 10 or more brain injuries and who have the ApoE4 gene tend to have worse cognitive outcomes than those lacking the gene [9].

Modifiable Alzheimer’s risk factors

(i) Obesity

Obesity is a proven risk factor for Alzheimer’s disease. A study that tracked 1500 people for 18 years concluded midlife obesity more than doubles the risk for Alzheimer’s disease [10].
(ii) Type 2 diabetes

Type 2 diabetes is connected to higher Alzheimer’s risk. In diabetes, hyperinsulinemia almost doubles the risk for Alzheimer’s disease compared to people without diabetes [11]. There is also good evidence of hyperinsulinemia accelerates functional cognitive decline [12]. Furthermore, insulin resistance is implicated in the pathogenesis of AD [13].

(iii) Homocysteine

An elevated blood level of homocysteine, a metabolic of methionine, is a risk factor for Alzheimer’s disease [14]. Comprehensively research studies connected homocysteine to increase Alzheimer’s risk [15]. Documenting many studies indicating vitamins B₆, B₁₂ and folate can effectively lower homocysteine.

(iv) Cardiovascular abnormalities

Poor brain circulation has been more closely linked to vascular dementia than to AD, many cases of an AD are complicated by the presence of micro-lesions denoting blood vessel breakages mini strokes [16].

(v) Hypertension

Hypertension at midlife is linked to significantly increase the risk for AD [17].

Signs and symptoms

The patient normally visits the physician at the behest of his family. The family typically detects an example of changing behaviors that can include following signs and symptoms

- Memory problems
- Insomnia
- Anxiety
- Depression
Memory impairment is the characteristic indication of Alzheimer’s disease and normally involves behaviors such as forgotten engagements, puzzlement away from home, misplaced items, and repetitive questions. The memory impairment of Alzheimer’s patients are defined as the condensed ability to learn novel information and to recollect previously learned information.

Alzheimer’s disease has been classified into three stages.

- Stage one generally lasts two to four years. It involves forgetfulness, confusion, disorientation, mood changes and recent memory loss.
- Stage two frequently lasts two to ten years. It characteristically is characterized by decreased memory functioning, reduced attention span, hallucinations, wandering, restlessness, muscle spasms, reduced ability to perform logic, increased irritability, and an increased inability to organize thoughts.
- Stage three generally lasts one to three years. This stage most often involves the increased incapability to identify family members, a progressive incapacity to recognize their own image in the mirror, incontinence, weight loss, swallowing difficulty and development of skin infections.

**Diagnosis**

The most extensively accepted diagnostic criteria for likely Alzheimer’s disease (AD) were developed by the U.S. National institute of neurological and communicative disorder and stroke (NINDS), AD and related disorders association joint working group. The diagnosis of AD is based on the presence of confirmed memory impairment and the
presence of single or additional of the following three cognitive deficits:

- Apraxia (impaired ability to bring out certain motor behaviors)
- Aphasia (verbal communication impairment)
- Agnosia (failure to identify or recognize objects in the surroundings)
- Impairment in executive functioning (the ability to organize, plan and abstract).

The physicians need to verify that above deficits are not caused by other nervous system condition such as Huntington’s disease, Parkinson’s disease (PD), brain tumor and cerebrovascular disease. The patients in the early stages of Alzheimer’s will frequently make errors in the recall of items in a simple memory test.

A physician might order a lumbar puncture if a chronic central nervous system CNS infection is suspected. Standard laboratory examinations in patients presenting with suspected Alzheimer’s include following tests.

- Complete blood cells counts
- Glucose levels
- Serum electrolyte levels
- Serum vitamin B12 test
- Liver tests
- Kidney function tests
- Thyroid tests

The electroencephalogram (EEG) is a useful instrument in the diagnosis of Alzheimer’s. Those with the disease have a symmetrical and diffuse slowing of the brain waves that register on the EEG. A computed tomography scan or magnetic resonance imaging may also be performed to rule out mass lesions, hydrocephalus, and to confirm the presence of
the atrophy of brain tissue.

**Fig.1.1.2. Differentiation of a normal (left) and Alzheimer’s patient's (right) brain.**

If a person affected by Alzheimer’s, certain brain cells become inactive and lose their ability to perform specific tasks. This leads to cell death and degeneration of the brain. The brain’s folds mean outer layer was shrunken and the grooves are conspicuously broadened. Brain mass is condensed up to one-third, attributable to a significant loss of nerve cells, synapses, and dendrites. The majority of this circuit failure occurs in the neocortex [18]. Comparing the healthy brain suffers merely modest loss of mass through aging [19]. This is shown in fig.1.1.2 in which disease spreads from healthy brain to an Alzheimer’s brain.

**Fig.1.1.3. Schematic representation of Alzheimer’s spreads in the brain.**

A: Plaques and tangles in normal brain areas involved in memory, B: progressively spreads to brain areas and C: Ultimately much of the brain is affected.

The brain of individuals with Alzheimer’s has an abundance of plaques and tangles.
Plaques are deposits of a protein fragment called β-amyloid that builds up in the spaces between nerve cells. Tangles are twisted fibers of another protein called tau that builds up inside cells. Alzheimer’s disease causes microscopic changes in the brain concerning abnormal clumps (amyloid plaques) and tangled bundles of nerve cell fibers (neurofibrillary tangles) made up of misplaced proteins. There is also an extensive loss of nerve cells (neurons) in the cerebral cortex. This loss is somewhat higher in the frontal and temporal areas. This loss causes the brain to atrophy (shrink). The annihilation and death of nerve cells cause personality changes, memory failure problems in carrying out daily activities and other symptoms of Alzheimer’s disease and schematic representation of Alzheimer’s spreads in the brain was shown in fig.1.1.3. The dramatic loss of synapses and degeneration of cholinergic cells results in the reduction of acetylcholine (ACh), which is believed to play a vital role in the cognitive impairment associated with Alzheimer’s disease. The recent study showed that acetylcholinesterase (AChE) plays role in accelerating αβ plaques deposition. Thus, the cholinergic hypothesis has become the leading strategy for the development of anti-Alzheimer’s disease agents which are inhibitors of acetylcholinesterase (AChE) [20].

The treatment of Alzheimer’s disease has progressed and shifted since the late 1970s to a transmitter replacement strategy. There has been no cure so far to stop Alzheimer’s disease, while only symptomatic treatment is available. The pathology of Alzheimer’s disease consists of a combination of genetic and non-genetic multi-factors. Between them, one theory named as “the cholinergic hypothesis” has been suggested leading to a discovery of “acetylcholinesterase (AChE) inhibitors”. The most effective treatments are
the medications that attempt to increase the brain’s levels of acetylcholine, an important neurotransmitter whose levels decrease with the onset of the disease. Elevation of acetylcholine levels in the brain through the use of AChE inhibitors has been accepted as the most effective treatment strategy against AD [21].

Cholinesterase is a family of enzymes that catalyze the hydrolysis of the neurotransmitter acetylcholine into choline and acetic acid, a reaction necessary to allow a cholinergic neuron to return to its resting state after activation.

Cholinesterase has two types

- Acetylcholinesterase (AChE) also known as acetylcholine acetylhydrolase.
- Butyrylcholinesterase (BuChE) also known as plasma cholinesterase, acylcholine acylhydrolase, butyrylcholinesterase.

Therefore, Acetylcholinesterase (AChE) and butyl cholinesterase (BuChE) inhibitors have become the drug of choice in the management of Alzheimer’s disease [22]. Several acetylcholinesterase AChE inhibitors named as cognitive enhancers are being investigated for the symptomatic treatment of Alzheimer’s disease. In our research, we aim to put focus particularly on the Acetylcholinesterase inhibitors compounds used in the treatment of Alzheimer’s disease.

1.2.1. A role of acetylcholine and acetylcholinesterase for the Alzheimer’s disease.

Acetylcholine

The chemical compound acetylcholine (often abbreviated ACh) is a neurotransmitter in both the peripheral nervous system (PNS) and central nervous system (CNS) in many organisms including humans. In the peripheral nervous system, acetylcholine (ACh) is the neurotransmitter at the neuromuscular junction between the motor nerve and skeletal
muscle. In the central nervous system, acetylcholine is found primarily in interneurons, and a few important long-axon cholinergic pathways have also been identified.

Nerve cells in the brain communicate to each other by releasing chemicals, these chemicals are called neurotransmitters. Acetylcholine is significant neurotransmitters for memory. Peoples with Alzheimer’s disease contain low levels of acetylcholine in their brain. It is chiefly found at neuromuscular junctions and cholinergic system, where its activity serves to terminate synaptic transmission. Acetylcholine slows the heart rate when functioning as an inhibitory neurotransmitter. Though, acetylcholine also performs as an excitatory neurotransmitter at neuromuscular junctions [23]. The mechanism involved in cholinesterase inhibitor drugs involves the blocking breakdown of ACh, therefore elevating ACh levels at the cholinergic synapses and reimbursing for loss of cholinergic circuits [24]. During neurotransmission, acetylcholine (Ach) is released from the nerve into the synaptic cleft and binds to ACh receptors (nicotinic and muscarinic) on the postsynaptic membrane, relaying the signal from the nerve. AChE, also located on the post-synaptic membrane, terminates the signal transmission by hydrolyzing ACh. The liberated choline from the ACh decomposition is taken up again by the pre-synaptic nerve and the neurotransmitter is synthesized by combining with acetyl-CoA through the action of choline acetyltransferase. (Shown in fig. 1.2.1. and fig. 1.2.2.)

![Chemical mechanism of acetylcholine formation.](image)

**Fig.1.2.1.** Chemical mechanism of acetylcholine formation.
Acetylcholinesterase (AChE)

Acetylcholinesterase also was known as AChE or acetylcholine acetylhydrolase is an enzyme that degrades (through its hydrolytic activity) acetylcholine in the brain. If their action is inhibited, more acetylcholine is available for communication between the nerve cells. Acetylcholinesterase is a serine hydrolase mainly found at neuromuscular junctions and cholinergic brain synapses. Its significant biological role is termination of impulse transmission at cholinergic synapses by rapid hydrolysis of the neurotransmitter ACh to acetate and choline. Acetylcholinesterase has an extremely high catalytic activity each molecule of AChE degrades about 25000 molecules of acetylcholine per second. The choline produced by the action of AChE is recycled, transported, through reuptake, back into nerve terminals where it is used to synthesize new acetylcholine molecules [25].
1.3. A brief review of drugs treatments for the AD as acetylcholinesterase inhibitors.

There is a considerable amount of medical research that is currently taking place to discover efficient therapeutic treatments for Alzheimer’s disease. Acetylcholinesterase inhibitor drugs stop or slow down enzymes from breaking down acetylcholine when it passes from one cell to another. This signifies that the acetylcholine, which is, in short, delivery in people with AD is not damaged so rapidly and there is extra chance of it being passed on to the next nerve cell. Regions of the brain that depend principally on cholinergic circuitry are normally the first and most harshly damaged by Alzheimer’s disease [26].

Acetylcholinesterase inhibitors consequence in higher concentrations of acetylcholine, leading to augmented communication between nerve cells, which in revolve, may momentarily stabilize or improve the symptoms of dementia. The employ of cholinesterase inhibitors is only one potential pharmaceutical approach to treat the signs and symptoms of Alzheimer’s disease. The effect of these cholinesterase inhibitor drugs differs for different people. Some people will not feel any effect and some may find that their symptoms improve slightly and others will remain the same when they would have expected their symptoms to become gradually lower. There is no way to find how an individual will respond. The areas in which some people with Alzheimer’s disease may find enhancement are:

- Memory
- Role in daily activities.
- Aptitude to think clearly.
- Psychological symptoms.
➢ Behavioral symptoms.

There is a substantial amount of drug research that is currently taking place to find out effective therapeutic treatments for Alzheimer’s disease. The current medical administration of Alzheimer’s disease has approved some drugs. The drugs in a class called cholinesterase inhibitors are used in the treatment of Alzheimer’s disease, U.S Food and Drug Administration (FDA) approved Acetylcholinesterase inhibitors were donepezil, tacrine, galanthamine and rivastigmine [26].

**Donepezil**

![Structure of Donepezil](image)

**Fig.1.3.1. Structure of Donepezil.**

Donepezil acts as a centrally acting reversible acetylcholinesterase inhibitor [27]. It is a drug that binds and reversibly inactivates the cholinesterases, thus inhibiting hydrolysis of acetylcholine. This results in an increased acetylcholine concentration at cholinergic synapses. Some clinical studies state that donepezil improves cognitive function in patients with severe Alzheimer’s disease symptoms as well. It is obtainable as a disintegrating tablet and oral solution, being 100% oral bioavailability with no difficulty crossing the blood-brain barrier (BBB) and slow excretion. Donepezil emerges to be the most effective and best tolerated.

**Side effects:** Gastrointestinal anomalies, bradycardia, abdominal pain nausea, diarrhea and anorexia [28, 29].
Tacrine

![Structure of Tacrine](image)

**Fig.1.3.2. Structure of Tacrine.**

Tacrine is a centrally acting anticholinesterase inhibitor and indirect cholinergic agonist. The drug that acts to increase the concentration of acetylcholine in the brain. It was the first centrally acting prototypical cholinesterase inhibitor approved for the treatment of Alzheimer's disease in 1993. Its immediate successor, approved for all stages of Alzheimer's disease. Recent studies found that patients taking tacrine need to have liver monitoring on a weekly basis because of its potential to damage the liver. It also acts as a histamine N-methyltransferase inhibitor [30].

Side effects: Nausea, vomiting, salivation, sweating, bradycardia, hypotension, collapse, convulsions and liver toxicity [31, 32].

**Rivastigmine**

![Structure of Rivastigmine](image)

**Fig.1.3.3. Structure of Rivastigmine.**

Rivastigmine is an acetylcholinesterase inhibitor; it is the consideration to work by inhibiting cholinesterase enzymes which would otherwise break down the brain neurotransmitter acetylcholine [33]. It is a parasympathomimetic or cholinergic agent for the treatment of mild to moderate dementia of the Alzheimer’s. The drug is administered orally as capsules or liquid formulations, with good absorption and bioavailability of
about 40% in the 3 mg dose. It is eliminated through the urine and has relatively few drug-drug interactions. Early and continued treatment of AD with rivastigmine maximizes the observed beneficial effects in the rate of decline of cognitive function, activities of daily living and severity of dementia with daily doses of 6 to 12 mg.

Side effects: Bradycardia, nausea, diarrhea, and anorexia [34, 35].

**Galantamine**

![Galantamine structure](image)

**Fig.1.3.4. Structure of Galanthamine.**

Galantamine used as a cholinergic enhancer in the treatment of Alzheimer’s disease. It is an isoquinoline alkaloid that has been isolated from the bulbs and flowers of *Galanthus woronowii* (*Amaryllidaceae*) known as “snowdrop” [36].

Galantamine completely inhibits acetylcholinesterase (AChE) enzyme which hydrolyzes acetylcholine. As a result of acetylcholinesterase (AChE) inhibition increases the availability of acetylcholine for synaptic transmission [37].

Side effects: Bradycardia and nausea.

**1.4. Alternative approaches to Alzheimer’s disease prevention**

There is rising evidence that lifestyle, including a diet rich in antioxidant, neuroprotective and anti-inflammatory agents might diminish the risk of developing Alzheimer’s disease. The Mediterranean diet, known for first and foremost as a way to protect against heart disease, may decrease the incidence of Alzheimer’s disease. This diet, along with others, may help prevent the development of Alzheimer’s disease by possibly scavenging
reactive oxygen species, intensification the ability of neurons to protect themselves. The alternative therapies to Prevent Alzheimer’s disease were follows.

**Diet Therapy**

There is accumulating evidence that diet is important in the prevention and control of Alzheimer’s disease. One of the main concerns in an Alzheimer’s patient is to maintain sufficient nutrient intake and prevent malnourishment. Research indicates a diet high in carbohydrates is more appealing to the Alzheimer’s patient and will lead to improved levels of food intake. The Mediterranean diet that involves the high intake of monounsaturated fats, wine and cereals has been connected with an increased risk of cognitive decline.

**Nutritional Therapy**

**Vitamin E**

Vitamin E is a renowned antioxidant that is a good candidate to stop or halt the progression of the characteristic biological processes linked with Alzheimer’s disease. Newer evidence in animal studies has further confirmed the importance of vitamin E deficiency in the development of Alzheimer’s disease [38]. An epidemiological study has found that vitamin E has strong effects against oxidative processes in the brain and that the collective use of vitamin E and vitamin C reduced the occurrence of developing Alzheimer’s disease by 64% over a lifetime [39].

**Vitamin B12**

A newer study found that vitamin B12 deficiency in patients who already have AD is more likely to have a diversity of neuropsychological disorders than those with more normal levels of vitamin B12 in the blood [40]. A study found that vitamin B12 levels are
significant in the prevention of Alzheimer’s disease, but the researchers found that once Alzheimer’s disease develops, vitamin B12 supplementation is of little benefit in the control of the disease [41].

**Folic acid**

Folic acid is known to play a very important role in a variety of biological processes in the body. Folic acid deficiencies have been linked with the development of depression. A study of depressed patients found that 31-35 percent of the individuals were folic acid-deficient [42]. This type of depression is more common in the elderly. The correction of folic acid deficiencies in these elderly patients often results in the correction of depression [43]. Depression is also one of the most common presenting symptoms of Alzheimer’s disease.

**Dehydroepiandrosterone (DHEA)**

Dehydroepiandrosterone is the most common hormone in the body. It also found in large quantities in the brain. A case-control study found that a group of 14 persons with Alzheimer’s disease had considerably lower levels of DHEA sulfate in the plasma compared to 13 matched healthy controls [44]. A new study of patients with Alzheimer’s disease found that the administration of DHEA sulfate combined with insulin improved a variety of physiologic factors associated with the Alzheimer’s disease [45].

**Zinc**

Zinc deficiency has been quoted as a factor in the development of Alzheimer’s disease [46]. Zinc is involved in a wide variety of cellular processes, particularly in the formation of enzymes critical to the replication of DNA and in the creation of proteins. Zinc is also a significant factor in antioxidation processes. It is generally accepted by scientists that
Alzheimer’s disease caused by oxidation processes. Insufficient quantities of zinc in the body could be associated with the destruction of nerve cells and the formation of plaques and tangles that is associated with Alzheimer’s. A study of 10 Alzheimer’s patients who were given 27 milligrams of zinc daily found that 8 patients had specific improvement in social behavior, comprehension ability, and communication skills, memory performance [47]. Additional research is needed to determine the suitable dietary levels of zinc to prevent Alzheimer’s disease.

**Phosphatidylcholine**

Researchers have found that phosphatidylcholine a key substance found in lecithin, supplementation can lead to increased levels of acetylcholine in the brain. This would propose that phosphatidylcholine would be effective in treating Alzheimer’s disease. A new study has provided evidence that phosphatidylcholine breaks down at a faster rate in Alzheimer’s disease patients than in healthy persons [48]. This proposes a role for phosphatidylcholine supplementation in Alzheimer’s patients. A new study found that a combination of vitamin E, pyruvate, and phosphatidylcholine provides more protection against brain oxidation processes in dementia-type diseases than vitamin E alone [49].

**Antioxidants**

Alzheimer’s disease is a process characterized by oxidative properties. Therefore, antioxidants, in general, should have positive effects in both the prevention and treatment of Alzheimer’s. A study found that antioxidants such as vitamin A, vitamin D, lycopene, and beta-carotene were all significantly lower in Alzheimer’s disease patients than controls [50]. The most excellent studied of the remaining antioxidants is vitamin C. A case study found that plasma vitamin C levels are lower in patients with Alzheimer’s
disease and that these levels are associated with the degree of cognitive impairment [51]. A prospective study of 633 patients aged 65 years and older found that high-dose supplementation with vitamin C reduced the risk of developing Alzheimer’s disease [52].

**Music Therapy**

Numerous studies have demonstrated that music therapy provides positive effects to Alzheimer’s patients. A study of 18 elderly Alzheimer’s patients aged 55-95 years with severe disease found that music played during bath time led to significant decreases in aggressive behavior events over a two-week period [53]. A study found that music therapy produces a variety of behavioral, stress, and immunological effects that are associated with positive memory changes in Alzheimer’s disease patients [54].

**Therapeutic Touch and Massage therapy**

The researchers found that the therapeutic touch therapy significantly reduced discomfort in Alzheimer’s patients. A study that measured anxiety and dysfunctional behavior in Alzheimer patients found that expressive physical touch combined with visualization led to decreased anxiety and dysfunctional behavior in advanced Alzheimer patients [55]. A different study found that both therapeutic touch and hand massage reduced agitation levels in these patients [56].

**Exercise Therapy**

Exercise therapy can decrease the risk of developing Alzheimer’s disease [57]. An additional study of older subjects found that exercise reduces the risk of developing vascular dementia and Alzheimer’s disease [58].

**Miscellaneous therapies**

A new study of acupuncture combined with music therapy found that this combination
approach improved a variety of measures in AD patients [59]. The commonly-used sleep-inducing agent melatonin has also shown some positive effects in the AD. A new study has found that melatonin reduces the negative effects of amyloid beta proteins [60]. A new study has found that the progression of AD symptoms can be slowed down by social networking [61].

The major spotlight of new drug development has been intended towards to find out AChE inhibitors. There is still a need to develop further proficient drugs for Alzheimer’s disease. Consequently, a need for progress and utilization of alternative anticholinesterase compounds with fewer side effects leads to an investigation on plants a possible source of treatment. Plants have been used since ancient times in the treatment of several diseases including cognitive disorders, such as Alzheimer’s disease. We hope that all these research in finding new drug molecules for Alzheimer’s disease may still continue to focus on medicinal plants and herbal originated drugs may lead to the discovery of novel medicines. A lot of other new approaches to treatment are also under investigation worldwide. We don’t yet know which of these strategies may work, but scientists say that, with the essential support, the outlook is excellent for major breakthroughs in the near future.
1.5. References


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