REPUBLIC OF TURKEY

FIRAT UNIVERSITY

GRATUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

EVALUATION OF THE POSSIBLE NEUROPROTECTIVE EFFECTS OF *ACHILLEA BIEBERSTEINII* (ASTERACEAE) PLANT ESSENTIAL OIL ON SCOPOLAMINE-INDUCED AMNESIC RATS

SALAM ABDALLA HASSAN

Master's Thesis

Department of Biology

Supervisor: Prof.Dr. Eyup BAGCI

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CONTENTS

Pages

ÖZET

***Achillea biebersteinii* (Asteraceae) bitkisinin uçucu yağının scopolamine ile olusturulan amnezik ratlarda olasi nöroprotektan etkilerinin değerlendirilmesi**

Bu çalışmada, *Achillea biebersteinii* Afan (Asteraceae) uçucu yağının olası nöroprotektan özelliklerini araştırdık. Bu bitki bir çalı olup güney-batı Asya, güney-doğu Avrupa ve kuzey Afrika'da yayılmıştır. Bitki tibbi ve aromatik bitki olup Türkiye'de ve Dünya'da tibbi ve aramatik bitki kullanılmaktadır. Klasik tıpta kanamalar, iştahsızlık, astım, mide ağrısı ve tümörlerin tedavisinde kullanılmaktadır. Bu araştırmada *Achillea biebersteinii* (Asteraceae) uçucu yağının skopolaminle oluşturulan amnezik ratlarda hafıza geliştirici, anksiolitik ve antidepresan etkileri değerlendirilmiştir. Hafıza oluşumu için y-labirenti ve radyal-kol labirenti testleri kullanılmıştır. Bunun gibi, anksiyete ve depresyon-benzeri davranışlar yükseltilmiş artı labirenti ve zorunlu yüzme testleri ile ölçülmüştür. Skopolamin uygulanan ratlar beklendiği üzere hafıza oluşumunu azaltıp, anksiyete ve depresyona yol açmıştır. Ayrıca, skopolamine uygulaması ratların hipokampüs ve amigdala homojenatlarında kontrolle kıyaslandığında süperoksit dismutaz (SOD), glutatyon peroksidaz (GPX), ve total glutatyon içeriğini (GSH) azaltmış, malondialdehit (MDA) miktarını ise artırmıştır. *Achillea biebersteinii* uçucu yağı skopolamin uygulanan ratlarda hafıza gelişimini anlamlı olarak artırmış ve oksidatif stresi azalttigi saptenmiştir. Böylece, bu çalışmada *Achillea biebersteinii* uçucu yağı uygulamalarının skopolaminle oluşan hafıza zayıflığını amigdala ve hipokampüs homojenatlarında oksidatif stresi azaltarak düşürdüğü saptanmıştır.

Anahtar Kelimeler: *Achillea biebersteinii* uçucu yağı, Nörodejeneratif Hastalıklar, Alzheimer Hastalığı, Skopolamin

ABSTRACT

In this study, we investigated the possible neuroprotective effects of *Achillea biebersteinii* Afan (Asteraceae*)* volatile oil. The plant is a shrub, distributed in South-west Asia, South-eastern Europe, and Northern Africa. It is an aromatic and medicinal plant and used for this purpose in Turkey and the World. In conventional medication, it is prescribed for treating haemorrhage, in-appetence, asthma, stomachache and tumours. The present research investigates the memory enhancing, anxiolytic and antidepressant effects of *Achillea biebersteinii* essential oil on scopolamine-induced amnesic rats. Y-maze and radial arm maze tasks were used for evaluating memory formation. Likewise, the anxiety and depressive-like behavior were conducted by elevated plus-maze and forced swimming tasks. The scopolamine-treated rats reduced the memory formation, and caused anxiety and depression as expected. Furthermore, scopolamine administration decreased the activities of superoxide dismutase (SOD), glutathione peroxidase (GPX) and the total content of glutathione (GSH), while increasing malondialdehyde (MDA) levels in the rat amygdala and hippocampal homogenates of the rats as compared to control. *Achillea biebersteinii* volatile oil significantly enhanced memory development and reduced oxidative stress in scopolamine-treated rats. Hence, this study suggests that the multiple exposures of *Achillea biebersteinii* volatile oil ameliorates scopolamine-induced spatial memory weakness by reduction of the oxidative stress in the rat amygdala and hippocampus homogenates.

Key words: *Achillea biebersteinii* Essential Oil, Neurodegenerative Diseases, Alzheimer's Disease, Scopolamine.

LIST OF FIGURES

Pages

LIST OF TABLE

Page

1. INTRODUCTION

The Application of medicinal plants with volatile oils has been rising. Aromatic plants and volatile oils are utilized as part of pharmaceutical and chemical application additionally in medicine for blending of different sanative formation (Redzig et al., 2006). There has been developing the interest for the identification of the natural products from plants for the detection of new antioxidant agents and antimicrobial. Additionally an alternative path for the substitution of manufactured chemicals, side effects of which are always in question. For this, the volatile oils and the extracts of numerous plants have been arranged and screened for their antimicrobial and anticancer activity, the number of reports in the literature concerning the aforementioned properties of plants (Sokmen et al., 2004). In a previous couple of years, various studies have concentrated on the potential use of volatile oil formulations in biological control of different insect pest and illnesses. The essential oils which get more quickly degraded into nature than chemical mixes have been studied for their activity against different insect pest of stored products (Patnaik et al., 2011; Bazzoni et al., 2002). The volatile oils are worthy natural products utilized as crude materials, as a part of numerous fields, contain perfumes, cosmetics, aromatherapy, phytotherapy, flavours and sustenance (Buchbauer, 2000). Unadulterated mixes isolated from aromas and complex essential oils have been demonstrated to impel a several of impacts on human and other mammalian species (Carvalho-Freitas *et al*., 2002).

The term “essential oil” is a contraction of the original “quintessential oil.” This stems from the Aristotelian idea that matter is composed of four elements namely, fire, air, earth, and water (Baser and Buchbauer, 2010). Volatile oils have numerous medicinal characteristic, in herbal medicine, they are utilized for their antibacterial characteristic against contagious sickness of the fungal source and against dermatophytes those of bacterial origin (Mehani and Ladjel, 2012). Herbs have the wide capacity to synthesis fragrant materials essentially secondary metabolites (Kashani et al., 2012). In various example, it is described that the production and composition of the volatile oil of every species have been influenced by various factors. For example, physiological varieties, natural conditions, geographic varieties and hereditary agent (Mehrsorosh et al., 2014). These varieties are of special significance in the study of biological and pharmacological activity of these products, as the rate of a volatile oil in aromatherapy has to be associated with its chemical composition (Lahlou, 2004). Volatile oils are complex blends

containing numerous single mixes. Each of these components contributes to the useful or adverse impacts of these oils. Therefore, the intimate knowledge of volatile oil compound allows for a better and especially regulate application (Buchbauer; 2000). Herbal volatile oils perform an essential role in conventional medication in a few countries (Omran and Esmailzadeh, 2009). In various cases, these herbal materials serve as protect particle against microorganisms, bugs, and herbivores (Kashani et al., 2012). Essential oils got from flavours, herbs and therapeutic plants by distillation, expression or dissolvable extraction are well known in conventional pharmaceutical that is considered to be an area of enthusiasm as a potential source of antimicrobial factor. They are portrayed by an expansive spectrum action, including antifungal, antibacterial and antiviral activities. Moreover, antimicrobial activities of volatile oils, they utilized as a part of nourishment conservation, sustenance industry as enhancing, pharmaceuticals, in cosmetics as aromatic and alternative medicine (Tarek et al., 2014).

Neurodegenerative sickness are a consequence of hereditary changes and ecological components which are firmly related to age (Sheikh et al., 2012). Mitochondrial dysfunction and oxidative stress perform an essential function in the development of the more common neurological disease.Loss of mitochondrial role is related to an increase in the formation of responsive oxygen intermediates and various individual disorder (Van Houten et al., 2006). Mitochondria dysfunctional not just contribute to neurodegeneration through the production of reactive oxygen species additionally as key agent in apoptotic pathways (Vadnal, 2012). Metals have a crucial function in neurodegeneration.While transition metals are important in numerous biological responses, change in their homoeostasis result in an increased free radical produce, which is catalysed by iron, copper, or other follow redox active metals. In all cases, metal-mediated oxidative stress is additionally related to mitochondrial dysfunction. The increase of iron in the brain related to various neurodegenerative sicknesses may cause an increased formation of free radicals by means of the Fenton reaction (Sheikh et al., 2012).

Excitotoxicity is the process by which brain cells are destroyed and damaged because of extreme stimulus by neurotransmitters, for example, glutamate. In normal neuronal signalling, an activity potential is transmitted down the axon of a nerve cell by saltatory conduction until it arrives the terminal button of the axon. After arriving the

button, depolarization from the activity potential causes ion channels to open, permitting calcium (Ca^{+2}) to enter the cell. The increase in intracellular calcium causes vesicles containing neurotransmitters to join with the layer of the presynaptic terminal and discharge neurotransmitter into the synapse. The discharged neurotransmitter then adhere to receptors situated on the layer of the postsynaptic terminal, leading to the opening of ion channels on the postsynaptic terminal. The opening of ion channels leads to an influx of calcium and an alter in membrane potential. Whenever enough stimuli happen, an activity potential is generated in the postsynaptic cell. Any unused neurotransmitter is immediately expelled from the synaptic cleft by means of transport channels situated on the presynaptic layer or astrocytes or inactivated. If there is dysfunction with the reuptake component, or in the capacity of the cell to properly lead to nerve motivations (because of demyelination), an abundance amount of the neurotransmitter will remain or be discharged into the synaptic cleft. In the case of glutamate, the overabundance neurotransmitter causes an intemperate entrance of calcium into the postsynaptic neurone. This overabundance calcium can then activate various chemicals including phosphatases, endonucleases, and proteases, all of which lead to cell damage and dysfunction, additional complicating the excitotoxic state. Moreover, excessive calcium can also activate the mitochondrial permeability transition (MPT), by causing mitochondrial permeability transition pores to open. The opening of the MPT pore leads to mitochondrial dysfunction, which prompts the formation of reactive oxygen species and a decrease in ATP levels. Without ATP, calcium pumps fail to pump calcium out of the cell, leading to an influx abundance of intracellular calcium. Continued with calcium entrance leads to further mitochondrial dysfunction and enactment of pro- apoptotic pathways (Vadnal, 2012 ; Matute et al., 2001).

Alzheimer's disease For the first time discovered since 100 years previous, however, study into its signs, causes, risk factors and treatment has obtained momentum just in the most recent 30 years (Alzheimer’s Association, 2013). In 1906 by Alois Alzheimer, a German neurologist and therapist, AD was found (Bethune, 2010). In spite of the fact that the aetiology of Alzheimer's disease is yet not totally known, numerous factors are considered to perform crucial roles in Alzheimer's disease pathogenesis. These incorporate low levels of acetylcholine, oxidative stress and free radical production, the dyshomeostasis of biometals and β-amyloid (Aβ) sediments (Sang et al., 2015). Numerous scientist thinks that AD, such as other common chronic illnesses, develops as a

consequence of various factors rather than an only cause. In AD, these many factors are an assortment of brain alteration that may start 20 or more years since sign appear (Alzheimer's Association, 2013). When a people has the manifestations of dementia, for example, memory or dialect difficulty, a doctor will direct tests to recognizes the cause. various reasons for dementia are related with distinct signs style and brain distortions (Association, 2016). In AD brains, severe neurodegenerative modifications happen. Loss of neurones and neurotransmitters, atrophy, and the particular consuming of neurotransmitter systems, for example, acetylcholine in the hippocampus and cerebral cortex are within these alterations (Aydin et al., 2015).

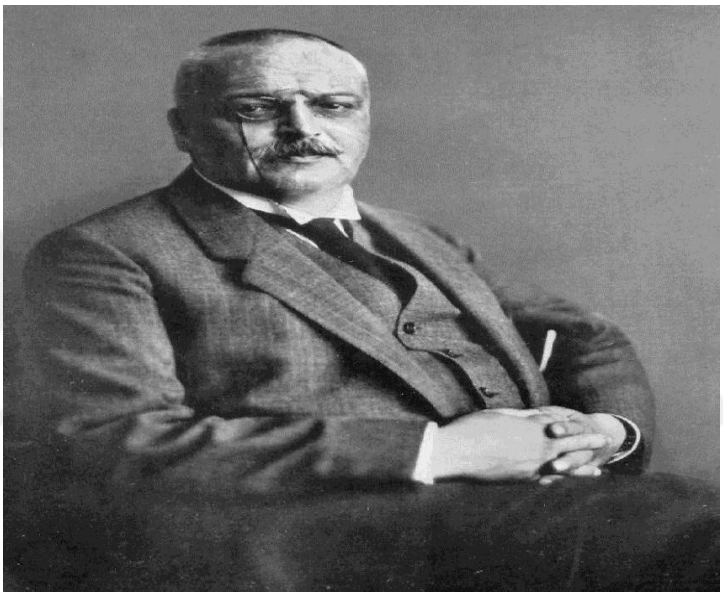


Figure 1. Alois Alzheimer (1864-1915) (URL-1).

AD is multifactorial and, up to now, an irreversible neurodegenerative sickness with an aetiology and neurotic pathway that remain mostly unknown (Soultanov et al., 2016). As the aetiology of idiopathic AD is unknown, animal models have depended on the use of hereditary mutations related to familial AD (FAD), with the rationale that the incidents downstream of the initial trigger are entirely similar (Laferla and Green, 2016). In Alzheimer's disease patients, neuroinflammation is perceived as an early abandon in the pathogenesis (Eikelenboom et al.,2010). Despite the function of neuroinflammation in the Alzheimer's disease brain remains unclear, discoveries from laboratory disease models and clinical research have presented a significant increase of inflammation to neurotic characteristic and signs of Alzheimer's disease (Takeda et al., 2014).

New studies have detected that synaptic dysfunction or loss may happen shortly in AD and can be regarded as the important basic for defensive treatment to slow down Alzheimer disease development and protect cognitive capacities (Wang et al., 2007). Because the start of AD is insidious, numerous patients with AD are not detected when manifestation are mild. The Canadian study of health and ageing demonstrated that between cases living in the community, 11% have mild Alzheimer's disease, while 89% have moderate to severe Alzheimer's disease (Zhu and Sano, 2006). Presently, no successful medicines for AD are accessible (Bagci et al., 2015). Prior published information indicated that oxidative stress is participatory in Aβ(1-42) causes neurotoxicity and the pathogenesis of AD (Hritcu et al., 2015). It is understood that oxidative stress has a major function in the etiopathogenesis of AD. One of the many agreeable hypotheses for Alzheimer's disease embroilment onset that mitochondrial impairment and oxidative stress is one of the main occasions in the insurgency of the pathology (Picone et al., 2014).

Epidemiologic and biochemical information indicate a connection between cholesterol, amyloid precursor protein, Aβ, and Alzheimer's disease. Two new epidemiologic studies suggest that there is a diminished prevalence of AD relate with the utilization of cholesterol-lowering medications that inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase (Simons et al., 2001). Also, other epidemiologic studies show that individuals with risk factors, for example, hypertension, diabetes, cerebrovascular sickness and elevated cholesterol are two times more tending to evolve Alzheimer illness than those without vascular risk factor (Nicola-Antoniu, 2013). A private relationship amongst Framingham cardiovascular risk (FCRP) and dementia, with respect to both disease and epidemiological perspectives, has been depicted, yet different research have not affirmed a connection between the score and cognitive deterioration (Viticchi et al., 2015). AD usually causes complexity, for example, stability, and difficulty swallowing. These can cause malnutrition and raise risk of pneumonia, resulting death in these patients (Bethune, 2010).

It is important to identify cognitive weakness at the soonest to improve the effective of the therapy option (Lue et al., 2016). The clinical investigation of Parkinson's disease (PD) requires various motor hallmark to be established, although subtle motor signs might be available, a clinical investigation of PD can't be made until they become

clearer (Noyce et al., 2016). To date, an extensive variety of physical treatment modalities has been suggested and utilized to treat motor debilitation in PD (Picelli et al., 2016). Idiopathic PD weakens working memory, but the accurate of this nature deficit in terms of the underlying cognitive mechanisms is not surely known. while just around 20% of patients with idiopathic PD improve frank dementia (Gruszka et al., 2016). Microglia activation is a histopathological sign of various neurodegenerative sicknesses, including PD (Kim et al., 2000). PD includes adjustments of the extrapyramidal nervous system, which organize stance and voluntary motion, and is identify by symptoms, for example, resting tremors, inflexibility and akinesia (Vecchis et al., 2016).

Various research has shown the relationship of PD with previous analysis, for example, depression, stress, constipation and erectile dysfunction (Noyce et al., 2016). Pervasiveness rates of depressive disorders in PD that are declared in the literature differ extensively, ranging from 2.7% to more than 90% (Reijnders et al., 2008). Summarised 44 education finding that depression rates vary from 7-70%. Variation in the classification, demonstrative devices, demographic qualities, test size and seriousness of Parkinson's disease may contribute to the variety in depression rates (Chen et al., 2007). Increased information on correlated and risk components of depression in Parkinson's disease, consequently, its easiness to the early detection (Zhu et al., 2016). The cause of PD has been an exporter of serious investigation since James Parkinson's first reported and, as with most illnesses, the pendulum has variably affected among nurture and nature (Lang et al., 2016). New studies demonstrated weakened attention and executive function influence complex motion in PD patients particularly the instrumental action day by day living which is identified correlated to intact memory (Naeem et al., 2016). The weakness of feeling of smell is one of the early sign of PD and is seen in 85% of the case (Hely et al., 2008). Increased the risk of falling in patients the Parkinson sickness (Nyström et al., 2016) About 30% of patients with AD produce parkinsonism (Nuytemans et al., 2016). Weakly muscle strength has been found in late puberty in people diagnosed to have PD, 30 years later (Nyström et al., 2016). Through the most recent 10 years, a few studies have been completed to measurement cerebrospinal fluid total α-syn levels in PD and different parkinsonisms, with the major purpose to affirm its analytic value as biomarker of synucleinopathy (Parnetti et al., 2016).

The earlier investigation has shown that specific noradrenaline (atomoxetine) and serotonin (citalopram) reuptake inhibitors can increase reaction inhibition in a subgroup of cases with PD (Kehagia et al., 2014). Presented the primary role of noradrenaline in attention, learning and administrative function (Chamberlain and Robbins, 2013). New reports exposed that neurodegeneration in Parkinson disease has additionally been relating to dietary habits, where inadequacy of antioxidant molecule, for example, folic acid (Hritcu et al., 2011). The sickness itself is not deadly, but, it produces a gradual deterioration in motor capacity, which can cause disability and significantly raises risks of choking, pneumonia, and falling-related wounds, producing a checked lessening in future (Vecchis et al., 2016). Treatment of PD depends on symptomatic alleviation, with the exception of avoiding secondary parkinsonism that produced by neurotoxins (Chandra et al., 2006).

1.1.Medicinal plants

The utilized on of therapeutic plants by the population, as an alternative treatment to treat various sicknesses, has been a traditional practice for a great many years before Christ. For instance, the utilized on of poppy (*Papaver somniferum*) and marijuana (*Cannabis sativa*) has been reported for a long time about 4,000 years (Dutra et al., 2016). Medicinal plants (MPs) perform an important role in taking care of the requests of the conventional medicine markets, which are discovered both locally in the formation and in overseas markets and in the financial, social, cultural, and environmental sector of local communities. In spite of classical nature of the tradition, therapeutic plants still produce the premise of conventional or indigenous health systems and are describe for by the world health organization (Hishe et al., 2016). Additionally, the side effects correlated with the wide utilized on of the manufactured pharmaceuticals may cause to severe damages to large portions of human organs. Hence, to overcome this limitation of manufactured drugs, analysts have changed their focus towards therapeutic plants which are identified as rich sources of antimicrobial agents and are vastly utilized by various nations for therapeutic purposes. Traditionally utilized therapeutic plants are known to yield an assortment of mixes with medicinal properties, for example, antidiabetic, antioxidant, antibacterial, anti-inflammatory, antipyretic, gastroprotective impacts, and etc. These plants are rich in an extensive variety of secondary metabolites, such as tannins, terpenoids, alkaloids, flavonoids, phenols and quinine (Gupta et al., 2016).

Plant secondary metabolites contain a variety of biological constituents from both therapeutic and sustenance plants capable of improving individuals health. The exposure to these phytochemicals, containing phenylpropanoids, isoprenoids and alkaloids, through true dietary way, may increase health advantages, protection against the chronic degenerative disease, essentially, found in western industrialised nations, for example, tumour, cardiovascular and neurodegenerative sickness (Iriti et al., 2010). The conventional landmark in the worldwide medicinal industry evolution was the found of salicin (pain relieving and antipyretic) by Raffaele Piria, in 1832, from Salix alba. In 1839, the first basic change from salicin was done, salicylic acid to be utilized in the therapy of rheumatoid joint inflammation. From the salicylic acid, Felix Hoffman utilized on aspirin (acetylsalicylic acid) in 1897. Therefore, the famed and powerful medicinal industry Bayer in Germany was born, and in addition the main patent in the field of medications (Dutra et al., 2016).

Interest for conventional systems of medication and, specifically, plant pharmaceuticals, has expanded considerably in both progressive and developing nations in the recent decades. The most recent three decades have seen substantial development in herb and natural outcome markets over the world. High-speed rising exportation of therapeutic plants through the previous decade to the global interest for these result and in addition to conventional health systems. As registered by the secretariat of the convention on biological diversity, worldwide sales of herbal outcome utilise an expected US $ 60 000 million in 2002 (Hishe et al., 2016). In addition, perform an essential role in the production of some more complicated particles. It has been assessed that around 30% of the accessible treatment medicine are gotten from environmental sources, notably from plants and microorganisms. In some medicinal ranges, for example, oncology, the number of plant-obtain drugs accomplishes 60% (Dutra et al., 2016).

Despite therapeutic plants are the most vital source of life-saving medications for most of the world's populace. Plant secondary metabolites are financially critical as medications, aromas, pigments, nourishment added substances and pesticides (Khan et al., 2009). Drug discovery from restorative plants has developed to contain various fields of the inquiry and several techniques for study. The process commonly starts with a botanist, ethnobotanist, ethnopharmacologist, or plant environmentalist who collects and utilized the plant(s) of concern. The examples may include species with known biological action for

which dynamic compound(s) have not been isolated such as (conventional utilized plants medicine or may include taxa obtained randomly for a huge screening program. It is essential to regard the mental property rights of a given nation where to plant(s) of interest are obtained (Balunas and Kinghorn, 2005). A large number of these traditionally utilized plants have been scientifically assessed with results yielding today's significant drugs, for example, aspirin, digitoxin, morphine and quinine (Miller, 2010).

Medicinal plants commonly utilized as crude materials for extraction of the fresh component which utilized in the production of various drugs. Like on example of medicines, blood thinners, antimicrobials and anti-malaria medications, contain the component from plants. Additionally the active component of taxol, vincristine, and morphine separate from foxglove, periwinkle, yew, and opium poppy, respectively (Hassan, 2012). In lately years, the conventional system of the drug has grown a topic of worldwide significance. While present day drug might be accessible ingrown countries, herbal medicines (phytopharmaceuticals) have frequently maintained popularity for conventional and social reasons (Rahini, 2014).

Little is known about therapeutic plants hereditary variation and population structure in spite of their significance as a fragrant and restorative plant. Furthermore, the application of atomic technologies gives practically on unlimited amount of potential markers utilize as a hereditary device for plant genotyping and gene mapping. The current learning on polymorphism among people is tremendous from morphological aspect to the molecular level. Terms of hereditary distances between entities (e.g., populaces or cultivars) are seldom amazingly high, both sorts of information are alternative of the marker structure to apply for a specific application, and they rely on upon its simplicity of utilized and the specific purpose of the examination (Nabi, 2014).

1.1.1. *Achillea* Genus

1.1.1.1. Medicinal Importance and Distribution of *Achillea* Genus

The *Achillea* genus has a broad distributional area and the variety in oil composition might be influenced by various ecological factors, for example, plant hereditary sort, seasonality, and formative stage (Dehghan and Elmi, 2014). The genus *Achillea* incorporates around 140 species circulated in South-west Asia , South-eastern Europe and northern Africa. It's used on in different parts of the world (Akcin and Akcin,

2014 ;.Dastjerdi and Mazoji, 2015). Also, discover in the Northern Hemisphere, and usually known as yarrows (Dehghan and Elmi, 2014). Nineteen of *Achillea* species have been identifying and distributed in various topographical and environmental locales of Iran (Gharibi et al., 2015).

Figure 2. *A. biebersteinii* plant pictures, (URL 2).

A. biebersteinii, one of the many predominant, *Achillea* species in the mediterranean area, is a perennial herb with erect stems, 30-60 cm high, leaves over to 10 cm, radiate heads and extensive thick compound corymbs. *Achillea biebersteinii* Afan., regionally named Kiliç out and Sari çiçek in Turkish, is utilized as a conventional medicine for treat haemorrhages, inappetence, asthma, stomachache and tumour (Yildirim et al., 2015). The genus is said to be named after *Achilles*, who utilized *Achillea* sp. For healing fighters injured through the Trojan war (Bariş et al., 2006). Lately, the anti-cancer action of volatile oils separates from some *Achillea* species has been registered and demonstrated that can change macrophages action (Mirahmadi et al., 2012). *Achillea* species have been utilized in traditional remedy and sold in the herbal store. Herbal teas produce from some *Achillea* species are conventionally utilized for abdominal disorder and flatulence in various country. A mixture of the dry or crisp flowering herb is utilized by the Bedouin for the treatment of coughs, fragrant intense stomachic and anthelmintic (Abd-alla et al., 2015). A few utilizations of *Achillea* in folk pharmaceutical incorporate therapy of pain, aggravation, migraine and convulsive sicknesses (Bashi et al., 2012). Asteraceae were assessed for their antimicrobial and antioxidant agent action in vitro. The oil proves

more potent antimicrobial action than the extracts (Sokmen et al., 2004). Despite a lot of data is accessible on the restorative and biological properties of *Achillea* species, little is utilized about their herbicidal and insecticidal properties (Çakır et al., 2015). The level of action is dependent on the mix and rate of various parts instead of the amount of the basic component (Miller, 2010).

Furthermore, medicinal applications plants are utilized as flavours and added substances as a part of nourishment products, while essential oil and extracts of some species are utilized for the development of digestive teas and restorative products (Turkmenoglu et al., 2015). Essential oils of *A. biebersteinii* identified that is used to inhibitory influence seed germination and seedling development of a few weed types (Abu-Romman, 2011). It is registered for that the produce and synthesis of the volatile oil for every species have been influenced by various factors, for example, physiological diversity, natural conditions, geographic varieties and hereditary components (Mehrsorosh et al., 2014). Literature study reported that the previous examinations of the volatile oil got from *Achillea biebersteinii* was performed just air-dried plant material (Al-Jaber et al., 2014). Investigation on the volatile oil combination of various *Achillea* species prompts the ID of numerous chemotypes in these plants in view of the significant chemical factor (Mirahmadi et al., 2012). prior studies have demonstrated that the *Achillea* genus has numerous active synthesis, for example, monoterpenes, sesquiterpenes, flavonoids and caffeoylquinic acid derivatives (Demirel et al., 2014).

1.1.1.2. Taxonomical and Morphological Features of Genus *Achillea*

The genus *Achillea* refers to the family Asteraceae which is the biggest group of vascular plants. *Achillea* is represented to by more than 140 permanent herbaceous species around the world, 47 species grow in Turkey, twenty-four of which are the endemic (51%) (Turkmenoglu et al., 2015). Subfamily Asteroideae, tribe Anthemideae. Anthemideae include 109 genera and around 1740 sp (Akyalçin et al., 2011). Achene micromorphological characteristic has been discovered important in systematics of the family Asteraceae (Akcin and Akcin, 2014). Little capitula framing level group at the highest point of the stem and hairy fragrant leaves are trademark for the genus (Turkmenoglu et al., 2015). Cypselae external morphology and life systems in individuals

from various tribes of Asteraceae are discovered essential for delimitation of species (Garg and Sharma, 2007).

1.2. Essential oils

Essential oil is more effective than different synthetic antimicrobial agents that utilized for air disinfection due to its low poisonous quality level and high volatility particular property that is not found in other antimicrobial agents (Inouye et al., 2003). Plant oils and extracts have been utilized for an extensive assortment of purposes for some thousands of years (Suganya et al., 2012). Volatile oil production in the plants is highly related to climatic conditions, particularly time length, irradiance, temperature, and water supply (Baser and Buchbauer, 2010). Newly, scientists have assessed that there are around 400,000 types of plants around the world, including around a quarter or a third have been utilized by organisations for therapeutic purposes (Mehani and Ladjel, 2012). Medical and fragrant plants are utilized by 70 % to 80 % of the worldwide populace for their medicinal impacts (Sharafzadeh, 2013). Medical plants have been utilized as conventional medicines for various human contagion for a large number of years around the world (Varposhti et al., 2013). Albeit medicinal plants have been utilized abundantly as a part of therapeutic, alimental, hygienically and enhancement businesses; there is few examination centred on their application for control of plant infections (Gholam, 2011). This requires the examining new classes of sheltered and more active antimicrobial factor by doing with various systems. Various plants containing secondary mixture could have some of these perfect protective property chiefly due to their antioxidant, antimicrobial, and other biological potentials (Bakkali et al., 2008). Biotechnological apparatuses are crucial for the increase and hereditary improvement of the therapeutic plants by adopting systems, for example, in vitro recovery and hereditary transmutation (Tripathi and Tripathi, 2005).

Various essential oils can progress the penetration of different medications through living membranes, for instance, the skin. The increase of the penetration can be accomplished by the interaction of the essential oils with liquid crystals of skin lipids (Baser and Buchbauer, 2010). Those plants, which give new and one of a kind scents and fragrances, have the potential for commercialization as new yields either as culinary herbs, aromatic teas or as sources of extractable essential oils (Juliani et al., 2004). Volatile oils,

as results of distillation, are blends of for the most part low atomic weight synthetic material. Sources of volatile oils incorporate components (e.g., mash, bark, peel, leaf, berry, and bloom) of organic products, vegetables, flavours, and different plants. Volatile oils produce from sustenances and non-nourishment sources. A large portion of the around 100 volatile oils utilized as flavouring substances as a part of nourishment are gotten directly from sustenance (i.e., lemon oil, basil oil, and cardamom oil), far less are extracts from plants not normally devoured as nourishment e.g., cedar leaf oil or amber fir oil (Baser and Buchbauer, 2010).

The history of the extraction of natural products goes back to Mesopotamian and Egyptian times, where the production of aromas or pharmaceutically volatile oils and waxes was the main business (Rahini, 2014). Volatile oils are inadequately dissolvable in water and this causes numerous problems for studying their biological and pharmacological properties. To solve these problems, numerous writers have advised to the utilization of different solvents in the dilution of volatile oils, for example, acetone, alcohol, ethylene glycol, ethanol and methanol (Lahlou, 2004). Pharmacological impacts of an essential oil rely on the contribution of its different components, the system of activity of a compound blend is significantly more complex than a simple sum of every component's physiological result (Baser and Buchbauer, 2010). Impacts of essential oils and fragrances on memory function and learning have less often been investigated than impacts on more primary cognitive functions (Baser and Buchbauer, 2010). Numerous studies analyses the impact of essential oils on various memory associated variables in Adults (Moss et al., 2003; 2008).

Essential oils could be in responsible for several of the positive health impacts reported by the user of the conventional medication. A high percentage of conventional products include teas made either by decoction or infusion (Foyet et al., 2011). Which are known methods for the extraction of volatile oils and their components (Miller, 2010). Plainly the volatile oil substance and composition of therapeutic and aromatic plants, thus their biological activities, are impacted by both inherent and external factors , for example, hereditary background, climatic conditions, plant development stages and sort of plant part, further post-harvest processing of plant materials and technique for extraction (Mirahmadi et al., 2012). Essential oils are usually results of rather complex compositions utilized contemporaneously as aromatherapy, and for centuries as aromatic medicinal

plant species in conventional systems of medication. Aromatic formulas are utilized for the therapy of an assortment of sicknesses, including those that influence the central nervous system (Almeida et al., 2004). Consequently, central nervous system recordings have been utilized by various scientists on an assortment of essential oils and aromas to discover impacts of odours on the human brain along the activation-relaxation continuum (Baser and Buchbauer, 2010).

1.3. Neurological diseases

A neurodegenerative disease is characterized by deterioration, usually irreversible, of the mental and cognitive ability and it is commonly correlated to elderly and additionally AD, PD and stroke (Iriti et al., 2010). Neurology is concerned with sicknesses correlate to the functioning of the nervous system. These sicknesses may existent acute or chronically, have transient or advanced courses, and influence an assortment of the anatomical area and cell kind. They are realized through various systems, including cell-autonomous dysfunction, unregulated protein collection, autoimmune situation, or vascular pathology (Jensen et al., 2013). Neurological dysfunctions that are distinguished by progressive loss of or decrease in intellectual capacities are known as dementia. Among different dementia sorts, AD is the most prevalent and the most serious one which estimates (60-80) % of dementia in the old person. Alzheimer's disease was not taken into evidence as a main known health disorder until the 1970s because medium lifetime of people was insufficient to identify the sickness widely (Çokyilmaz, 2011). Neurodegenerative dysfunction describes to themselves with their known hereditary mechanisms as in familial types of the sickness or with their part of misfolded or aggregated proteins. Imperatively, numerous pathobiological similarity have been appeared to lie in the centre of "neurodegeneration" (Bredesen et al., 2006). More studies showed that proteins with changed physicochemical properties are sedimentation in the human brain in neurodegenerative disease (Kovacs, 2014). Most of the pathophysiological processes of neurodegenerative illness share the accumulation of associated proteins which is one of the features of the degenerative procedures. New advances in the information of these proteinopathies demonstrate that the same protein could contribute to various diseases, in this be indicating a general pathological method (Nieoullon, 2011). These proteins generally exhibit high preservation within species and are found near layers or are included in microtubule transport. α-Synuclein is a protein that is physiologically enriched

in presynaptic ends (Winner et al., 2011). A nosological division of neurodegenerative disease depends on clinical presentation, anatomical area and cell sorts influenced, conformationally changed proteins required in the pathogenetic model, and aetiology if known (i.e. hereditary varieties or procured pathways of prion sickness (Kovacs, 2014).

Neurodegeneration, is common, characterised by the progressive loss of function and the structure of a set of neurones in the different area of the CNS. This causes the loss of some major neurological impairments, for example, memory deficiencies, impaired motor functions and orientation. Neurodegenerative sickness, such as AD, Frontotemporal Dementia, PD or Amyotrophic Lateral Sclerosis have like pathobiological characteristic proposing possible atomic bond among them (Atabay, 2010). Neurodegenerative illnesses include a wide variety of sickness that shares the general property for the gradual loss of structure or role of neurones and glial cells in the brain and spinal cord. Numerous neurological illnesses are a consequence of neuronal loss, and glial cells are additionally included (Winner et al., 2011). Neurodegenerative illnesses are the multifactorial debilitating dysfunction of the nervous system that influences around 30 million people in the world (Sheikh et al., 2012). Neurones are terminally detached cells that have no mitotic action. They imagine far from their zone of the role and they take a long excursion move to their last destination in the nervous system. Subsequent to obtain their objective site, they finish their differentiation process and end isolating by resting in quiescent stage (Lee et al., 2009). Under neurodegenerative conditions, neurones don't be able to renew themselves and die during programmed cell death. It infers that neurodegeneration is not a reversible method (Unal, 2012). Most examples of neurodegenerative illness are not demonstrated by Mendelian inheritance of well-known hereditary variations, yet rather are thought to have a complicated aetiology with various hereditary and ecological factors contribute to susceptibility (Ramanan and Saykin, 2013). Systemically, loss of the abovementioned neurological activities frequently describes to themselves in the eclectic region of the neurological system. Cases in Alzheimer's disease originally and at first influences the entorhinal cortex and hippocampus, while Parkinson's happens in the substantia nigra gradually decrease the primary roles of the area (Atabay, 2010). The high ratio of polyunsaturated fatty acids existing in neuronal layer makes the brain tissues especially susceptible to lipid peroxidation responses produce the combination of cytotoxic aldehydes, for example, malondialdehyde and 4-hydroxynonenal (Iriti et al., 2010).

Neurodegeneration has been considered to be interaction of various agents including ecological and hereditary pre-disposition however redox metal abuse possesses major function as the many of the manifestations stems out from abnormal metall metabolism (Uttara et al., 2009). Neurological problems generally happen in the context an underlying systemic sickness, and these neurologic exhibitions are a repeated exporter of inpatient and outpatient neurological deliberation. In various patients, the neurological dysfunction is a manifestation of an earlier identified systemic illness or its treatment, while in many others the neurological disease is the presenting manifestation of a medical condition that has not yet been diagnozsed (Steven, 2013). Neuroprotection refers to the techniques and related to the mechanisms capable of supporting the central nervous system against neuronal damage because of both acute (e.g. stroke or trauma) and chronic neurodegenerative condition, for example, AD, and PD. Among these techniques, herbal drug may represent a significant source in protecting rather than in treatment of some CNS sickness, in correlation with a healthy style of life including right dietary mode and direct physical action (Iriti et al., 2010).

1.3.1. Alzheimer's Disease (AD)

Alzheimer's disease (AD) is the average age-related neurodegenerative dysfunction, is described by increasing the loss of personal capacity with a shortcoming and his capacity to execute (Park et al., 2015). Cognitive sign is characteristic of AD, non- cognitive signs are becoming increasingly significant because of the spread and dysfunctions they generate (Bagci et al., 2015). Non-cognitive signs , for example, confusion, hostility, sadness and psychosis, are usually seen in demented patients containing those with Alzheimer's disease, although cognitive impairment. This sign, known as "behavioural and psychological symptoms of dementia" , have been accounted for to happen in around 20% of Alzheimer's disease patients (Takeda et al., 2014). The clarification of these disorder hallmarks all through the brain is irregular, it follows a predictive model that is utilized for pathological staging (Arendt et al., 2015). Alzheimer's infection represents more than 70 % of all instances of dementia, so it is critical to distinguish changed risk for the sickness (Sudha seshadri et al., 2002).

The most generally recognized early sign of dementia is trouble in recollect last incidents. As the dysfunction develops, an extensive variety of different sign can appear,

for example, disorientation, temperament swings, perplexity, more severe memory damage, behavioural changes, troubles in talking and gulp, and problems with walking (Winblad et al., 2016). AD is the most well-known cause of senile dementia and influences 7 % of people above 65 years old and 40 % of people above 80 years (Daulatzai, 2015). Alzheimer's disease pathology gradually impact numerous brain areas beginning with the hippocampus, basic region involves in learning and memory, particularly spatial memory (Dao et al., 2015). Alzheimer's disease causes a requisite responsibility on people and their families and caregivers, as people with Alzheimer's disease require a high cost of human services, and in addition social and financial help (Darbà et al., 2014).

Alzheimer's disorder is characterised by the concurrence of aggregates of abnormal accumulation consists of 2 proteins: Amyloid-beta and tau, and of cell alteration containing neurite degeneration and loss of neurones and psychological function (Mondragon-Rodrıguez et al., 2012). Also, AD is described pathophysiologically by the existence of extracellular senile plaques, intracellular neurofibrillary tangles, synapse loss, astrogliosis, and inflammation. Senile plaques consist of an amyloid beta peptide (Aβ) centre surrounded by dystrophic neuritis (Sharafzadeh, 2013). Early discovery and analysis of Alzheimer's disease is a challenging task. The hippocampus shows the most percentage of atrophy in the early stage of the disease (Shen et al., 2012). Various studies suggest that senile plaques are related with neurodegeneration in AD, and (Aβ), a main extracellular part of senile plaques, is one of the key agents in the pathogenesis of AD (Son et al., 2015). Alongside those clinical hallmarks, enormous synaptic loss happens in the early clinical phases of AD, and this loss is well related to the cognitive deficit appeared in AD patients (Son et al., 2015). The extracellular Aβ plaques and intracellular neurofibrillary tangles describe to key neurotic symptom , yet are not necessarily, the first reason of neuronal toxicity (Tanghe et al., 2010). Investigations of Aβ peptides in cerebrospinal fluid (CSF) have consistently demonstrated that declining or low levels of Aβ 42 and Aβ 42/Aβ 40 rate and high concentrations of tau in patients with moderate cognitive impairment are related to great brain Amyloid-beta amount (Schupf et al., 2015). Amyloid-beta toxicity is correlated with increases in responsive oxygen species (ROS), included H2O2 (Hritcu et al., 2015).

The two basic pathological symptoms of AD are amyloid plaques and neurofibrillary tangles. The amyloid cascade suppositions indicated that the sedimentation of beta-amyloid (Aβ) triggers neuronal dysfunction and loss in the brain (Ballard et al., 2011). Stimulation is a histopathological hallmark of various neurodegenerative illnesses, including Alzheimer's infection (Kim et al., 2000). Astrocytes, the most abundant glial cell, perform a crucial function in neuronal care and in preserve homoeostasis inside the central nervous system (Maragakis and Rothstein, 2006). Stimulate glia surround and penetrate Aβ plaques in Alzheimer's disease (Mathur et al., 2015). Epidemiological studies produce information about the phenomenon for example(prevalence and incidence), clarification (eg, demographic, geological, and temporal varieties), determinants (eg, hereditary and non-hereditary risk or defensive components), health financial matters (eg, expenses of human services and cost viability of treatment and vaccination), and vaccination strategies (eg, healthy and preventive interventions) of Alzheimer's disease and another dementias (Winblad et al., 2016). Because the main risk factor for Alzheimer's disease is ageing, the prevalence of the infection rises dramatically with old age inhabitance around the world (Winblad et al., 2016). As lifetime expectancy increases, a number of Alzheimer's disease patients rise consequently, which due to a heavy socioeconomic responsibility. As of now utilized medicines offer a little symptomatic assistance in mild to moderate Alzheimer disease, however, can't postpone or prevent the progress of Alzheimer's disease (Cho et al., 2012). The neuropathologic signs of AD brains are extracellular aggregation of diffuse and neuritic amyloid plaques, include of amyloid-β (Aβ) peptide, and often surrounded by dystrophic neurites and the intraneuronal aggregation of neurofibrillary tangles composed of hyperphosphorylated protein tau (Cacace et al., 2016). Alois Alzheimer (1907) was the first who explained the neurofibrillary tangles in the soma of cortical neurones in a 51-years of age lady who had a 5-year history of gradual dementia (Cvetkovic-Dozic et al., 2001). Neurofibrillary tangles are a main pathologic sign of Alzheimer's disease. neurofibrillary tangles are intraneuronal inclusion bodies that comprise of an aggregation of double helical fibres, which biochemically are fundamentally comprised of abnormally phosphorylated tau (Wisniewski and Fernando, 2014).

1.3.1.1. Clinical Symptoms of AD.

AD Symptoms changes among individuals (Alzheimer's Association, 2015). Clinically, there are distinctive scales used to the feature the different phases of Alzheimer's disease. However, it must be emphasised that it's really a progressive, continuous deterioration (Feuk, 2002). The early stages of Alzheimer's disease cannot be distinguished from some characteristic related to normal ageing. More than 50% of the population above the age of 65 (Alzheimer's Association, 2015). A few individuals with memory problems have a case called amnestic mild cognitive impairment. Individuals with this case have more memory troubles than healthy for individuals their age, however, their signs are not as severe as those found in individuals with AD (Adear Center, 2011). General signs contain forgetfulness, communication challenges, and alteration in the mood and behavior. The person in this stage a remember multiple of their practical capacities and need minimum help (Canada, 2013) .

In moderate AD stage, destroyed happen in the region of the brain that controls language, reasoning, nervous processing, and conscious thought. Memory loss and trouble deteriorate, and individuals start to have the problem remember family and mate. They might be incapable of learning new things, doing assignments that include several steps, for example, (get dressed up), or cope with the new condition. They may have hallucinations delusions, paranoia, and may behave carelessly (Adear Center, 2011). The most general primary sign is progressively worsening capacity to recognize new. This happens because that the primary neurons to die and failure is normally neurons in brain areas participate in forming new memories (Alzheimer's Association, 2013).

The last stage is called severe Alzheimer's disease, patients need continuous help. Talk becomes short to some intelligible words. If patients survive, deterioration continues to a point where they cannot sit up, lose the capacity to laugh, show increased physical rigidity and develop reflexes typical for the child e.g: grip and sucking reflexes. The most common cause of death is pneumonia (Feuk, 2002).

1.3.1.2. Causes of Alzheimer's

The reason for AD is not accurately known, the "amyloid hypothesis" is the most greatly discussed and investigated hypothesis about the reason for Alzheimer's disease. In

this amyloid theory, the primary reason for Alzheimer's sickness comes from neurotic plaques which are caused by the abnormal settlement of a protein called beta-amyloid. Beta-amyloid is really separated from a much bigger protein particle known as the amyloid beta precursor protein (APP). Both amyloid beta precursor protein and A-beta are available in healthy brains, although their role is still under analysis. The chief problem in Alzheimer's sickness is that abnormally high result of A-beta cumulated in the brain, overpowering the enzymes and the different particle whose task it is to clean it away. Also, the clearing away process itself seem to be defective. This applies even in the ageing brain, in which no less than two of the enzymes that help with A-beta become to gradually decrease whether Alzheimer's ailment is present or not. It is currently believed that the true risk comes when the individual A-beta molecule accumulates together to produce little poisonous accumulation called oligomers. In any case, the oligomers are come to produce neurotic plaques on the brain (Hampel and Blennow, 2004).

The other hypothetic causes of AD is neurofibrillary tangles. The "neurofibrillary tangles" to present them their full name, are produced of a protein called tau, which, similar to beta amyloid happens in healthy nerve cells, however, in Alzheimer's sickness it converts to be chemically changed and heaps up as a thread like tangles, reduce tau's key functions in nerve cells. One of these function is in nerve sprouting which is a significant characteristic of self-repair in the neural system. Another tau function is in preserve a sort of railroad track structure inside nerve cells that moves required chemicals and minor organelles up and under the nerve filaments between the cell body and the distant nerve endings called dendrites as shown in (figure 3), the cell body is the factory and substation for the whole nerve cell. This transportation method is necessary for the cell to operate and remain, and the tangles confuse it and in a sense choke the cells to death (Andreasen and Blennow, 2005). As a result of the progressive cumulation of these two proteins, neurofibrillary tangles and plaques are grown up and beginning deterioration in all cognitive and motor capacity of the casualty as influencing brain interferes with signalling at the neurotransmitters. Increase as a consequence of mutations to any of 3 particular genes. A hereditary mutation is an abnormal alteration in the chain of the biochemical couple that make up genes. These mutations include the gene of the APP and the genes for the presenilin 1 in chromosome 14. furthermore, presenilin 2 genes on chromosome 1. Those genetic mutations to the APP or presenilin 1 chromosome are ensured to progress

AD. Those genetical a mutation in the presenilin 2 gene have a 95 % person with chance of raising the sickness transformations in any of these (3) genes have a tendency to increasing AD sign before age 65, in some cases as early as age 30, while by wide majority of the people with AD have late-onset sickness, happening at age 65 or later (Goldman et al., 2012).

1.3.1.3. Pathological Hallmarks of AD

The pathological feature of Alzheimer's disease are the cumulation of extracellular Aβ as neuritic plaques and congophilic angiopathy, and also the intracellular cumulation of abnormally phosphorylated tau as neurofibrillary tangles (Wisniewski and Fernando, 2014).

1.3.1.3.1. Amyloid-β protein

The pathogenesis of AD is still indefinite in numerous respects. Research lead in the mid-1980s, demonstrating that senile plaques in AD brain tissue are Consists mostly of the sticky amyloid-beta, later make the proposition of the 'amyloid cascade hypothesis'. As per this theory, the cumulation of Aβ is the main event that leads to all consequent occasion in the pathology of AD (Nilsson, 2006). AD is histopathologically characterised by extraneuronal Aβ protein sediment. Historically,amyloid-beta, has been associated with cell poisonous and hereditary proof supplies the basis for its suggestion as the main reason of the sickness (Mondragon-Rodrıguez et al., 2012). The Aβ peptide, which is the main protein ingredient of diffuse and neuritic plaques, produce beta amyloid through proteolysis from the amyloid precursor protein (Laferla and Oddo, 2005) (Figure 4).

The amyloid hypothesis suggests that AD is caused by an imbalance between Aβ formation and removal, resulting in rises quantum of Aβ in different structures, for example, monomer, oligomer, insoluble fibrils, and plaques in the CNS. Large amounts of Beta-amyloid then start a cascade of occasions culminating in neuronal destruction and death manifesting gradual clinical dementia of the Alzheimer kind (Mawuenyega et al., 2011). If this theory is true, biomarkers designed to identify Aβ cumulation in preclinical populaces may have a significant role in the early detect of AD (Sperling et al., 2011). Found that though the association between Aβ deposits, neurodegeneration, and cognitive ability in elderly people were in partly consistent with current and hypotheses about the main role of Aβ in Alzheimer's disease change, the appearance of AD-associated

neurodegeneration without Aβ plaques in a few people recommends that different components of Alzheimer's disease pathology may additionally it's important through the preclinical phases of the sickness (Goldsworthy and Vallence, 2013).

The hallmark Alzheimer's disease pathology of β-amyloid plaque burden and neurodegeneration are found to a substantial proportion of cognitively healthy elderly individuals, Aβ deposition is found in 20–30% of cognitive healthy more elderly individuals (Wirth et al., 2013). The progression of neurodegeneration independent Aβ sedimentation of elderly people may indicate another component as being main through the preclinical phases of Alzheimer's disease (Goldsworthy and Vallence, 2013). In such respect it has been demonstrated that the Aβ accumulation/oligomerization method performs a primary function in pathogenesis; as it were, one soluble Aβ molecule (monomer) react with different Aβ monomers to produce dimers, oligomers, and polymers, every condition of accumulation producing a potentially pathogenic factor. Certainly, various conditions of soluble accumulates have been firmly associated with synaptic loss and cognitive weakness (Mondragon-Rodrıguez et al., 2012). All these pathological events are related to AD and most possible perform a role in the illness process, however, the formation and cerebral deposition of Aβ are still considered, by most researchers, important to the progression of this disease (Nilsson, 2006).

1.3.1.3.2.Tau protein

Tau a microtubule-connected protein commonly located to the axon, where it physiologically facilitates the axonal transport by attaching and stabilizing the microtubules as shown in (Figure 5). In AD, tau is translocated to the somatodendritic compartment and experiences hyperphosphorylation, misfolding, and accumulation, offering to ascend to neurofibrillary tangles and neuropil threads (Serrano-Pozo et al., 2011). Tau protein, located in both neuronal and non-neuronal cells, makes accumulation in neurones that compose one of the signs of AD (Bukar Maina et al., 2016). In its normal condition, tau is a soluble protein that encourages microtubule assembly and balancing. Pathological tau protein, by difference, displays modify solubility characteristic, produce filamentous structures and is abnormally phosphorylated at several residues (Laferla and Oddo, 2005). The abnormal phosphorylation of tau through AD is both associated with a rise in kinase action and/or a reduction in phosphatase action (Mondragon-Rodrıguez et

al., 2012). In Alzheimer's disease, tau pathology is confined to neurones, however in certain different tauopathies, for example, the 4R tauopathies corticobasal degeneration (CBD) and dynamic supranuclear paralysis, tau inclusions are additionally recognized in glia (Laferla and Oddo, 2005). Despite most thinking in the field propose that tau pathology is downstream from Aβ deposition (Wisniewski and Fernando, 2014). The putative functions of tau contain stimulation of tubulin polymerization, stabilisation of microtubules (Khan and Bloom, 2016). Hyper-phosphorylation, loss of normal role and toxic gain of function are connected to a few neurodegenerative disease, including Alzheimer's sickness (Khan and Bloom, 2016).

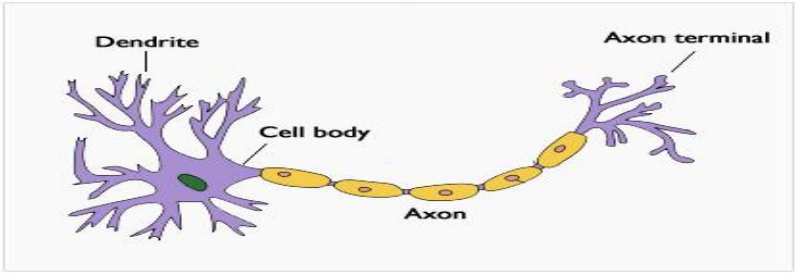


Figure 3. Neuron cell (Dendrites), (URL 3)

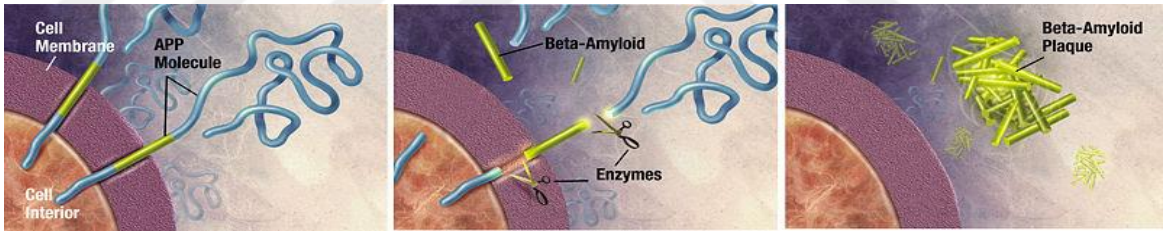


Figure 4. Amyloid-β protein,(URL 4) .

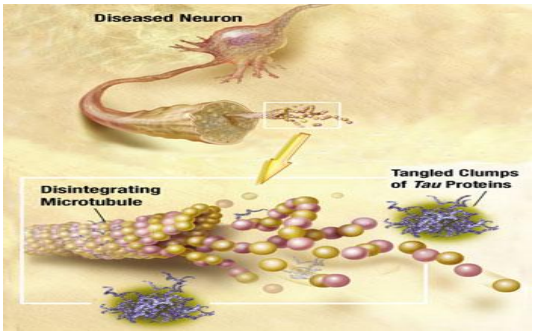


Figure 5. The illustration of Tau proteins, (URL 5)

1.3.1.4. Risk Factors for AD

Except for instances of AD-affected by hereditary abnormal, specialists think that AD, as other general chronic ailments, increased as a consequence of various agent rather than a solitary reason (Alzheimer's Association, 2015).

1.3.1.4.1. Age

The greatest of these three risk factors is age. Numerous individuals with AD are age 65 or more. Individuals younger than 65 can have AD, however, they are much less possible to increase the illness than more adult people.As age rise, so does the chance of having AD. For instance, 15 % of those with AD are age 65–74, while 44 % are age 75–84. Despite more elderly is a risk factor, AD is not a normal component of maturing, and elderly alone is not adequate to create the Alzheimer's (Association, 2016).

1.3.1.4.2. Family History (FH) of AD.

A FH of AD is not needful for a people to develop the sickness. In any case, people who have a parent or sibling with AD will probably increase the sickness than the individuals who don't have a first-degree relation with AD (Alzheimer's Association, 2015). Individuals with a family history of AD, especially a parent, have a 4–10 times raised risk (Honea et al., 2012). Researchers indicate that family history risk are related to the separate feature in brain morphology structures that may perform subjects at higher risk for increasing Alzheimer's disease (Donix et al., 2012).

1.3.1.4.3. APOE 4 gene

Genes perform an essential role impacting the onset and altering the progression of Alzheimer's disease. In particular, inheritance of AD demonstrates an age-related dichotomy in which rare however very penetrant mutations transmitted in an autosomal prevailing way are in accountable for early (≤ 60 years) onset familia alzheimers disease, while general polymorphisms with low penetrances, for example, apolipoprotein E (APOE) ε4 allele, appear to have their most impact on the more common, later onset forms of the illness (Bertram and Tanzi, 2004). The E4 allele of the (APOE4), the main known hereditary risk factor for late-onset sporadic AD, contributes to familial clustering of the sickness (Donix et al., 2012). While APOE e4 is the most strong hereditary risk factor, genome-wide relationship research on having recognized various other sensibility genes

however with lower effects (Genet et al., 2011). APOE differentially regulates Aβ formation, accumulation and clearance in an isoform-dependent way. Also, apoE4 can contribute to risk of Alzheimer's disease pathogenesis and psychological decay likewise by Aβ-autonomous mechanisms including synaptic flexibility, neurovascular role and neuroinflammation (Liu et al., 2013).

1.3.1.4.4. Modifiable Risk Factors

In spite of risk factors, for example, age and FH can't be altered, other risk components can be altered or modified, to decrease risk factors for cognitive deterioration and dementia (Baumgart et al., 2015). Assessing the condition of the guide on the impacts of modifiable risk for cognitive deterioration and dementia determined that there is enough strong guide, from a population-based attitude, that control physical action and regulation of cardiovascular risk factor (particularly diabetes, corpulence, smoking and hypertension) decrease the risk of cognitive deterioration and may decrease the risk of dementia (Association, 2016).

1.3.1.4.5. Cardiovascular Pathology Risk Factors

Increasing data indicates that the health of the brain is firmly connected to the overall health of the heart and artery. The brain is fed by one of the body's wealthiest systems of blood vessels. A hygienic heart helps assure that sufficient blood is pumped through these arteries and hygienic artery assist that the brain is provided with the oxygen and nutritious rich blood it necessary to work normally (Association, 2016). Numerous factors that raise the risk of the cardiovascular sickness are also related to a great risk of dementia. These factors incorporate smoking (Anstey et al., 2007). Obesity in midlife (Anstey et al., 2011). And diabetes (Reitz et al., 2012). Also, rising evidence indicates that consumption a nutrition that useful the heart, for example, one that is lower in saturated fats might be related with decreased AD and dementia risk (Association, 2016).

1.3.1.4.6. Education

The person with less age of legal education is at higher risk for AD and another dementias than those with more age of legal education (Sando et al,.2008). A few investigators think that having more age of education increase a "cognitive reserve" that allow the person to better compensate for alteration in the brain that could result in signs of

AD (Stern, 2006). As per to the cognitive reserve theory, having more years of education increases the connections between neurones in the brain and enables the brain to compensate for the early changes of Alzheimer's. By utilizing the alternative path of neuron-to-neuron correspondence to finish a psychological task. Moreover, lowering educational accomplishment may reflect lower financial status (Association, 2016).

1.3.1.4.7. Social and Cognitive Engagement

New studies indicated that continue socially and psychologically dynamic all through life may help brain and perhaps reduce the risk of AD (Wang et al., 2012). Continuing socially and psychologically activity may assist increase cognitive reserve, but the accurate mechanism by which this may happen is unknown. More analysis is needed to better see how social and cognitive ability may impact biological system to decrease risk of Alzheimer's diseases (Association, 2016). Some individual studies have demonstrated that social activity, high social system, and a history of social connection are related to best cognitive role and decrease risk of cognitive impairment (Baumgart et al., 2015).

1.3.1.4.8. Traumatic brain injury (TBI)

Traumatic brain injury is the interruption of normal brain capacity produced by a blow or jar to the head or entrance of the skull by a remote object (Association, 2016). The individuals who experience rehashed head wounds, (for example, boxers, football players, and battle veterans) might be at an even higher risk (Baumgart et al., 2015). Around 75 % of traumatic brain injury are moderate, indicate that the subsequent confusion, disorientation or absence of knowledge endures 30 minute or less. Mild traumatic brain injury results in lost awareness or post-traumatic amnesia that lasts over 30 minutes, however, less than24 hours. In the event that loss of awareness or post-traumatic amnesia lasts 24 hours or more, the traumatic brain injury is viewed as extreme. mild and severe TBI raise the risk of progressive Alzheimer's infection. compared and no TBI, mild TBI is related to double the risk of progressive AD and other dementias, and severe traumatic brain injury with 4.5 times have the risk (Association, 2016).

1.3.1.5. Vaccination Strategies for Alzheimer's Disease

Traditional vaccination against contagious disease depends on the generation of cell and humoral immune response that play to defend the host from overt sickness despite

the fact that they don't induce sterilising immunity. All the more as of late, efforts have been made with blended accomplishment to produce treatment vaccines against an extensive variety of noninfectious sickness contain the neurodegenerative condition. After the indicate first report of successful vaccine prevention of development of an AD animal model in 1999 (Agadjanyan et al., 2015). The new generation of remedial vaccines, based on in-depth information on pathologic mechanisms or hereditary, holds out the promise of objective and specific treatments. Remedial vaccines being progressed can be widely classified into three sorts:1) vaccines that help a patient's normal resistant reaction, overwhelm pathogenic microorganisms or abnormal cell forms; 2) vaccines that down-manage an abnormal immune response in hypersensitivities, rheumatoid joint inflammation, and diabetes, for instance; and 3) vaccines that stimulate an immune response to a particular endogenous mediator of ailment, for example, in atherosclerosis, hypertension, or AD (Imbimbo, 2002). The use of vaccine strategies to treat neurodegenerative sicknesses, for example, AD will still hold hope. Both active and inactive vaccination immune response to decrease AD-like pathology and restored cognitive deficiency in transgenic rodent (Gelinas et al., 2004). Although the AD vaccine improvement has been focused to a great extent on Aβ, there is data that the tau protein, sometimes in conjunction with Aβ, perform an essential role in AD pathology (Marciani, 2015).

Tests did by Schenk and partner in 1999 were the first to establish that vaccination with the Aβ peptide could decrease the sediment of plaques in the brain of mice hereditarily altered to develop Alzheimer's disease with the symptoms similar to those observed in the individual. Various vaccine strategy has been suggested with the Aβ peptide as the goal antigen, utilizing employing murine models to assess particular humoral responses and present a prognosis of sickness develop. Vaccine strategies utilizing DNA or peptides against Alzheimer's disease in view of different methodologies have generally induced poor resistant response (the case with DNA) or antibodies with modest ardentness for the objective protein (the case with peptides) (Alves et al., 2014). A powerful action to control the epidemic of AD that influences worldwide 40 million individuals and that expected to multiply by the year 2040, would be active immunization or vaccination, a plan support by the appearance of natural immunity against Alzheimer's disease (Marciani, 2015).

1.3.1.6. Treatment of AD.

1.3.1.6.1. Pharmacological Treatment

None of the pharmacologic medicines (meds) accessible today for AD decrease or pause the harm and damage of neurones that lead to AD and cause the infection lethal. The 6 medications permitted by the United state food and drug administration for the therapy of AD temporarily increase signs by raising the number of chemicals called neurotransmitters in the brain, The effective of these medications differ from individual to individual (Association, 2016). During of 2002-2012 about 244 drugs for AD were examined in the clinical trials just one of the 244 drug successfully finished the clinical test and went on to receive acceptance from the food and drug administration (Cummings et al., 2014). In December 2014, the food and drug administration approved the 6th drug, which consolidates two existing food and drug administration approved AD medications and is for mild to the severe sickness. previous that, the last approval of an AD medication was in 2003 (Alzheimer's Association, 2013). There are two kinds of drug used to treat AD: acetylcholinesterase inhibitors (The general names for the cholinesterase inhibitors are donepezil, rivastigmine and galantamine) and N-Methyl-D-aspartate) receptor antagonists, The NMDA receptor antagonist is memantine (Alzheimer's Society, 2014).

1.3.1.6.2. Non-pharmacological treatment

Non-pharmacologic treatments are those that don't include the drug. Non-pharmacologic treatments are frequently utilized with the objective of preserve or developing the cognitive ability, the ability to play the action of everyday living or overall personal life. They additionally might be utilized with the objective of decreasing behavioural symptoms, for example, depression, apathy, wandering, sleep disorder, confusion and aggression. such as incorporate art treatment, activity based treatment and memory training (Association, 2016). The objective of non-pharmacological treatment is deceptively simple; to get a positive feeling and to preserve that positive feeling for whatever length of time that possible. clinically, this represent a challenge (Zeisel et al., 2000).

1.3.2. Parkinson's Disease

Parkinson's disease (PD) is the second so common neurodegenerative dysfunction, after AD, influencing about one million persons in the United States (Chen et al., 2007). PD is a gradual neurological dysfunction with average motor symptom and different non-motor symptoms containing neuropsychiatric signs, autonomic disorder, abnormal sense, rest dysfunction, and tiredness (Zuo et al., 2016). Patients with PD are generally incapacitated, presenting signs of muscular rigidity, weakened mobility, loss of equilibrium and tremor in rest (Picelli et al., 2016). PD result in the loss of dopaminergic neurones in the substantia nigra (Blochberger and Jones, 2008). The detection of dopamine as a neurotransmitter in the 1950s by Arvid Carlsson and partners result in the description the function of dopamine in the pathophysiology of PD (Blochberger and Jones, 2008). Characterisation of the non-motor hallmark is probably important for early detection of PD and the movement disorders Society (MDS) has new published research criteria for prodromal PD (Noyce et al., 2016). In previous studies in Parkinson's disease, regular relations have been discovered among depression and age, anxiety, a sleeping disorder and dementia (Rojo et al., 2006).

The weakness of walk, short and variable step length and destination have since been considered classic clinical characteristic in Parkinson’s disease (Bayle et al., 2016). Best clinical experience is the main factor in the identification of PD, although they might be inadequate in challenging cases. A true identification is essential for counselling and proper administration and for enrolment of patients with idiopathic PD in the clinical test, where the inclusion of patients with another determination could affect the consequence (Birman and Lorberboym, 2016). Sensual complaints, particularly pain, are one of the most recognised nonmotor manifestation, and more than one-fourth of PD patients experience " primary pain" associated with the dysfunction of the nociceptive method in the early phases of PD when motor signs are not notable (Levin et al., 2016). Special genes that are related to PD have been distinguished, only monogenic types of the disease are infrequent and routine examination is, so, no prescribed (Blochberger and Jones, 2008). The reason for PD is obscure. A specified ecological risk factor has not been recognized. Clear hereditary structures account 10 to 15 percent of cases or less. Rising age and male sexual are risk components around the world (Chandra et al., 2006).

There are three pathological feature of PD, the presence of Lewy bodies; neuronal death in the level compacta of the substantia nigra; and the loss of pigmented neurones (neuromelanin) in pigmented brain stem cores (Blochberger and Jones, 2008). A few studies report that the relative danger of progress dementia in Parkinson's disease is 2 to 6 times higher than that of the general population (Bouwmans et al., 2016). Gradual motor retrogradation produces dementia which very effects on nature life and produces problem to achieve responsibility of day by day living in Parkinson's disease patients (Naeem et al., 2016). It has been notifying for that diminished cerebrospinal fluid levels of α-synuclein and total tau are correlated with an increased seriousness of motor sign in PD patients (Zhu et al., 2016). Total brain atrophy rates from MRI information might be an instructive approach to quantify sickness rises in an impartial method, in spite of the fact that to date, just three studies have utilized such a methodology as a part of progressive supranuclear paralysis (PSP) and multiple system atrophy (Guevara et al., 2016). Concerning co-morbid dysfunction, both psychosis and cognitive weakness, are characteristic in PD (Chen et al., 2007). Hippocampal decay has been related to cognitive impairment, particularly poorer memory, in PD with and without dementia (Stav et al., 2016).

The atypical parkinsonian disorders are synucleinopathies and tauopathies, i.e., syndromes described by the abnormal sedimentation of the proteins α-synuclein and tau (Levin et al., 2016). In α-synuclein(α-syn) is the major doer in the pathogenesis of synucleinopathies, being the main factor of the Lewy bodies. Mutations of the α-syngene are associated with early-onset monogenic familial PD and are correlated to increasing risk for sporadic PD (Parnetti et al., 2016). Previous research has indicated the participate of small fibre pathology in the neurodegenerative method of PD. Skin biopsies from PD patients have uncovered peripheral deafferentation and sedimentation of phosphorylated α-synuclein in cutaneous olfactory and autonomic nerves (Lin et al., 2016). Not all PD patients with such a cognitive profile improve dementia and early distinctive proof of these patients with especially increased risk is, however, impossible with enough accuracy (Liepelt-Scarfone et al., 2011). Mild cognitive weakness is a general non-motor hallmark of PD. It influences various cognitive areas, for example, executive capacity, memory, consideration and visuospatial function (Kang et al., 2016). While its precise pathophysiology is unclear, rapid eye movement rest conduct confusion happens more

regularly in patients with the neurodegenerative disease than in the generic population, and particularly in patients with α-synucleinopathy, for example, PD compared with non-synucleinopathy (Kim et al., 2016). Rapid eye movement sleep behaviour disorder is feature by the loss of normal deliberate muscle atonia through rapid eye movement sleep, correlate with extreme motor movement while dreaming (Olson et al., 2000). Depression and stress in PD are common and often co-pathological, with the major effect on health result (Landau et al., 2016).

1.3.2.1. Clinical symptoms of Parkinson disease

The clinical symptoms of Parkinson's are divided into two group — motor feature and non-motor feature. The motor characteristic are tremor: fine rhythmic activity (frequency 4–6Hz) and usually one of the initial symptom of Parkinson's; at first observe in one upper limb and encompassing both upper limbs at final phase of the illness, Bradykinesia such as weakness of activity, commonly in the upper body, Hypokinesia: poorness of movement, and rigidity such as the sense of resistance to negative motion, which start unilaterally and advance to bilateral rigidity in final stage of Parkinson's (Jankovic., 2008 ; Blochberger and Jones., 2008).

Non-motor symptoms contain Neuropsychiatric sign such as dementia, gloom, anxiety, optical hallucinations. Autonomic such as constipation, uric incontinence, hyperhidrosis, sialorrhoea's, low blood pressure. Sleep trouble such as fast eye movement sleep behaviour trouble, anxious leg feature, narcolepsy and sensual signs such as pain (dystonic and non-dystonic) (Blochberger and Jones., 2008 ; Jankovic, 2008).

1.3.2.2. Causes of Parkinson's disease

The causes of Parkinson's yet largely unknown. despite the disease is more common in elderly, the risk factor for the development of Parkinson's is not only age. It has been indicated that a combination of hereditary susceptibility and exposure to ecological risk might cause Parkinson's. Many non-genetic risk factors for Parkinson's have been indicated, based upon considering pathogenic pathways. despite, a directory of a relationship among ecological risk factors and progress of Parkinson's is weak. Indicating ecological factors involve exposure to pesticides herbicides or heavy metals (manganese, copper) (Blochberger and Jones, 2008).

1.4. Animal Models of AD.

Animal models for learning and memory have importantly contributed to novel strategies for medication improvement and subsequently are a basic role of the evaluation of remedial (More et al., 2016). Major insights into the role of genes related to Alzheimer disease and correlated dementias have happened through analysed hereditarily altered animals. Despite none of the current models completely transcribe the complete range of this insidious human sickness, basic features of Alzheimer pathology and disease processes can be experimentally recapitulated. Hereditarily altered animal models have assisted advance our understanding of the basic mechanisms of sickness and have demonstrated to be priceless in the preclinical assessment of potential remedial interventions. Continuing refinement and progression to products next reproduction of animal models will facilitate successes in resulting more translational concordance between preclinical studies and human clinical trials and in the end lead to the foundation of novel treatments for clinical exercise (Laferla and Green, 2016). The functional estimating of Alzheimer's disease animal models should be additionally be based on a wide analysis of activity, sensorimotor role, exploration and stress. Some of these function, such as sensorimotor disturbances could influences, could impact the hippocampal-dependent behavioural test and thus influence the interpretation of outcome (Gumucio, 2014). Preclinical models in Alzheimer's disease have two purposes: to study the pathogenetic system and detect potentially effective medications, their mechanism of work and poisonous. There is no model ready reflecting every disordered symptom of Alzheimer's disease. Subsequently, the present models should be considered as animal models of a neurodegenerative disorder correlated with the neurotic alteration in AD, rather than proper AD models (Von, 2004).

1.4.1. Pharmacological Models

Wider application of pharmacological models would facilitate the development of the new medication for AD. The two major models currently utilized depend on the cholinergic and glutamatergic hypotheses of AD. Despite, they lead to some of the attention and memory weakness recognized in AD, they don't completely increase the Alzheimer's disease model. Some studies that utilized a combination modelling strategy, ie, the simultaneous administration of many medications with the purpose of impairing

various neurotransmitters or various side of a solitary system, have reported no or minor cumulative impact (Gilles and Ertlé, 2000).

1.4.1.1.Scopolamine Models

Scopolamine is considered to used different poisonous characteristic on the CNS. It offered lethality on the inhabitance and dendritic development of the infant neurones and immature granular cells in the dentate gyrus, which immediately produce in the damage of the hippocampal circuits that may predominantly be responsible for cognitive and memory deficiencies (Aydin et al., 2015). Scopolamine treatment might exert as a psychopharmacological model of AD (Bajo et al., 2015). Administration of scopolamine to rodent brain decrease acetylcholine in the hippocampus. The neurobiochemical way under impairment of learning obtaining with concerning to scopolamine treatment has been very much described and is associated with a reduce in central cholinergic neuronal action by means of obstructing the muscarinic receptors (Hsieh et al., 2003).

Scopolamine, a muscarinic cholinergic receptor antagonist, has been widly ranging to examine cognitive deficiencies in laboratory animals. After intraperitoneal dose of scopolamine, the cholinergic neurotransmission was blockaded, cause in cholinergic dysfunction and weaken cognition in rodent (Foyet et al., 2015). Additionally, it has been declared that memory weakness stimuli by scopolamine in rodents is related to changing brain oxidative stress status (Fan et al., 2005). Scopolamine importantly increases acetylcholinesterase activity and malondialdehyde level in the cortex and hippocampus (Hancianu et al., 2013). Despite, numerous neurotransmitter systems appear to be impacted by alzheimer's disease, the cholinergic dysfunctions have gotten specific regard and majority of the treatments for this infection are directed to this system. The acetylcholinesterase is a crucial enzyme that rapidly hydrolyses acetylcholine (ACh), organized the levels of this neurotransmitter in the synaptic cleft, the being involved in cognitive ability of learning and memory (Gutierres et al., 2014). Although scopolamine had the direct inhibitory impact on acetylcholinesterase activity in-vitro (Santos et al., 2012).

1.4.1.2. Atropine Model

Atropine is an anticholinergic. It acts by preventing the impacts of a chemical in the body in the nervous system, stomach, intestines, certain organs such as salivary organ,

urinary region, and another cell. Early discoveries begin to in the 1960s demonstrating deleterious impacts of medications that block cholinergic activity like atropine and scopolamine on memory in rats, and parallel guide for cholinergic dysfunction in AD consequently led to the formulation of the 'cholinergic theory of geriatric memory dysfunction' (Benedikz et al., 2009). The significance of cholinergic activity in the brain for learning and memory ability was first recognized more than 3 decades ago, when the relatively low dos e of specific muscarinic acetylcholine receptor antagonists for examples (the belladonna alkaloids scopolamine and atropine) were determined to induce temporary cognitive deficiency in young individual volunteers that resembled those seen in ageing (More et al., 2016). It is well established that cholinergic system perform a significant role in the memory ability (Roloff et al., 2007).

1.4.2. Surgical Models

1.4.2.1. Amyloid β model

It is very well recognized fact that creation of amyloid-beta (Aβ) plaques are different characteristic factor of Alzheimer disease and administration of Aβ peptide has been known for inducing memory death (More et al., 2016). In Alzheimer disease patients, rise level of extracellular Aβ amyloid and progressive sedimentation of neuritic plaques encompassed by dystrophic neuritis, astrocytosis and gliosis describe the pathological procedures condensed as amyloidosis in Alzheimer disease (Ghiso and Frangione, 2002). This model is very specific for the screening of drugs exerted in Alzheimer disease (More et al., 2016). The additional extension the temporary and parietal segment with high neuritic plaques sediment through the complete cortex and subcortical region at the latest phase of Alzheimer disease (Von, 2004). There are numerous biochemical pathways responsible for Aβ-mediated memory weakness. although, it has been unstable to ending which of these pathways are the most significant in the onset of Alzheimer's disease. Aβ-peptide- mediated inhibition of choline acetyltransferase (ChAT) to induce disorder of cholinergic neurones is one of the hallmark mechanisms of Aβ-peptide to start Alzheimer's diseases (Nunes-Tavares et al., 2012). It has been established that ceaseless infusion or intense injection of Aβ into the brain prompts cerebrum dysfunction caused by neurodegeneration and weakness of learning and memory basically the same as that found in AD (Desrumaux et al., 2013). Dose of Aβ into the third ventricle of the rat brain for 14

days stimulate Aβ accumulation in different regions e.g., hippocampus and cerebral cortex (Meng et al 2013).

1.5. Purpose of the Thesis

The main purpose of this study is to evaluate the possible neuroprotective activity of *Achillea biebersteinii* volatile oil on scopolamine-induced amnesia rats. Also, to evaluate memory formation by using Y- and radial arm maze tasks, the anxiety and depressive-like behavior were conducted by elevated plus-maze and forced swimming tasks. The chemical composition of *Achillea biebersteinii* essential oils were also identified and compared with the other medicinal plants results on the Alzheimer's disease. The effect of the *Achillea biebersteinii* volatile oil on oxidative stress status in rats amygdala and hippocampus homogenates caused by scopolamine is also evaluate.

2. MATERIALS AND METHODS

2.1.Plant Materials and Essential Oil Preparation

Aerial parts of *Achillea biebersteinii* was gathered in the flowering stage in Elazig, Eastern Anatolian Region, Turkey. The plant samples were identified and a voucher specimen was recorded and stored in the Herbarium of Firat University (FUH) for ready reference. The oil was extracted by hydrodistillation for 3 hr. using a Clevenger-type apparatus.

2.1.1.Chromatographic Analyses

The essential oil was analysed by GC-FID (Agilent 6890 GC) with a column of HP-5 MS (30 m × 0.25 mm i.d., film thickness, 0.25 μm) and detector in Plant Products and Biotechnology Research Laboratory (BUBAL), Firat University. The essential oil was analysed by GC-MS (Agilent 5973 N) and GC-FID (Agilent 6890 GC) with a column of HP-5 MS (30 m × 0.25 mm i.d., film thickness, 0.25 μm) and detector in Plant Products and Biotechnology Research Laboratory (BUBAL), Firat University. The sample was injected by splitting and the split ratio was 1:100. The GC oven temperature is kept at 70°C for 2 min and programmed to 150°C at a rate of 10°C/min and then kept constant at 150°C for 15 min to 240°C at a rate of 5°C/min. Helium was exerted as the carrier gas at a flow rate of 1 ml/min. MS were taken at 70 eV and a mass range of 35-425. Alkanes were utilized as reference points in the calculation of retention indices (RI). MS were taken at 70 eV and a mass range of 35-425. Individual components were identified by comparison with the retention index from the GC-MS NIST library.

2.2.Animals Modelling

42 male Wistar rats weighing 250 ± 50 g at the beginning of the task were used. The animals were housed in a temperature and light-controlled room (22°C, a 12-h cycle starting at 10:00 h) and were fed and permit to drink water ad libitum. The rats were separated into six groups (each group consists of 7 animals): (1) Control group received 0.9 % saline with 1 % Tween 80 treatment; (2) Scopolamine (Sco) - alone-treated group received 0.9 % saline with 1 % Tween 80 treatment, as negative control; (3) Diazepam alone treated group (DZP, 1.5 mg/kg) received 0.9 % saline with 1 % Tween 20 treatment, as positive control; (4) Tramadol alone treated group (TRM, 10 mg/kg) received 0.9 % saline with 1 % Tween 80 treatment, as positive control; (5) Scopolamine-treated group

received *Achillea biebersteinii* volatile oil 1 % (Sco+AEO1 %) and (6) Scopolamine-treated group received *Achillea biebersteinii* essential oil 3% (Sco+AEO3%). Control, DZP, TRM- and scopolamine alone-treated groups were caged in the same circumstance but in the absence of the tested essential oil. They were subjected to inhale 0.9% saline with 1% Tween 20 solution. They were treated in accordance with the guidelines of the animal bioethics of the act on Animal Experimentation and Animal Health and Welfare from Turkey and all methods were in compliance with Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for the scientific target.

2.2.1. Inhalation apparatus and drug administration

The inhalation apparatus composes of a Plexiglas chamber (50 x 40 x 28 cm). Two chambers were used, one for the control and scopolamine alone-treated animals, which were exposed to 0.9% saline with 1% Tween 80 solution and the other one for the experimental animals, which were exposed to *Achillea biebersteinii* volatile oil was diluted with 1% Tween 80 (v/v) *Achillea biebersteinii* volatile oil exposure (200 µl, either 1% or 3%) was by an electronic vaporizer (Oregon Scientific WS113) placed at the bottom of chamber, but without reaching of the animals. Regarding concentrations to be used in the pharmacological tests, we choose 1% volatile oil normally used in aromatherapy and a higher concentration (3%) to maintain the impacts (Gradinaru et al., 2014). Daily, for 21 continuous days, rats in the *Achillea biebersteinii* volatile oil groups were exposed to oil vapours for controlled 15 min. Chambers were always cleaned up (10 % ethanol solution). Scopolamine hydrobromide (Sigma-Aldrich, Germany) was used as negative control and was dissolved in an isotonic solution (0.9 % NaCl) and 0.7 mg/kg scopolamine was injected intraperitoneally (i.p.), 30 min before the behavioural tasks. Diazepam (Sigma-Aldrich, Germany) and tramadol hydrochloride (Sigma-Aldrich, Germany) were used as positive controls and were injected intraperitoneally (i.p.) in a volume of 1 ml/kg in laboratory rats, an hour before behaviorally tested.

2.2.2. Y-maze Test

Short-term memory was evaluated by spontaneous alternation behaviour in the Y-maze task. It was used in the present research which composes of (3) arms (35 cm long, 25 cm high and 10 cm wide) and an equilateral triangular central field. 15 minutes after the inhalation of Achillea biebersteinii volatile oil (AEO 1% and AEO 3%), rats were put at

the end of one arm and permitted in order to move freely through the Maze for 8 min period. An arm entry was calculated when the hind paws of the rat were completely inside the arm. Spontaneous alternation behaviour was described as entry into the whole (3) arms on consecutive choices. The maximum number of spontaneous alternation behaviours was the total number of arms entered minus two and percent spontaneous alternation was calculated like:(actual alternations / maximum alternations) X 100 (Hritcu et al., 2014). Spontaneous alternation behaviour is supposed to reflect spatial working memory, which was a form of short-term memory.

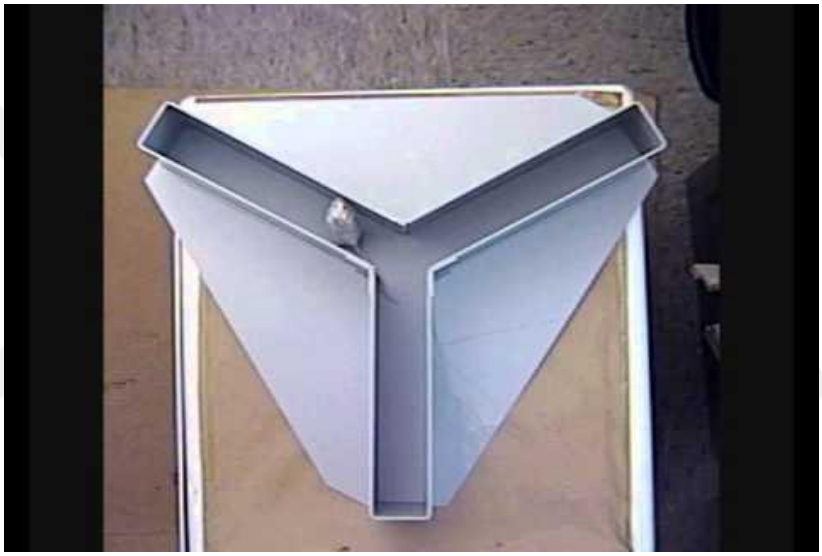


Figure 6. Y-maze test apparatus

2.2.3.Radial arm-maze test

The radial arm maze is used in the present study which consisted of (8) arms, and numbered from 1 to 8 (48 cm x 12 cm), extending radially from a central area (32 cm in diameter). The apparatus was placed 50 cm above the floor and surrounded by various extra-maze visual cues placed at the same location during this study. Before the actual training started, (3) or (4) rats were at the same time placed in the radial arm maze and permitted to explore for 5 min and take the food freely. The food was initially available throughout the maze but was slowly restricted to the food cup. The selection of the baited arms depended on the fact that animals prefer to solve the maze using an adjacent arm selection procedure. In this case, we change adjacent arm patterning behaviour by only

baiting 5 arms (nos. 1, 2, 4, 5, and 7) subjecting animals to change their strategy and far away from the unbaited arms. An arm entry was calculated when the paws of the rat were within an arm. Measures were made of the number of working memory errors (entering an arm containing food, but previously entered) and reference memory errors (entering an arm that was not baited).

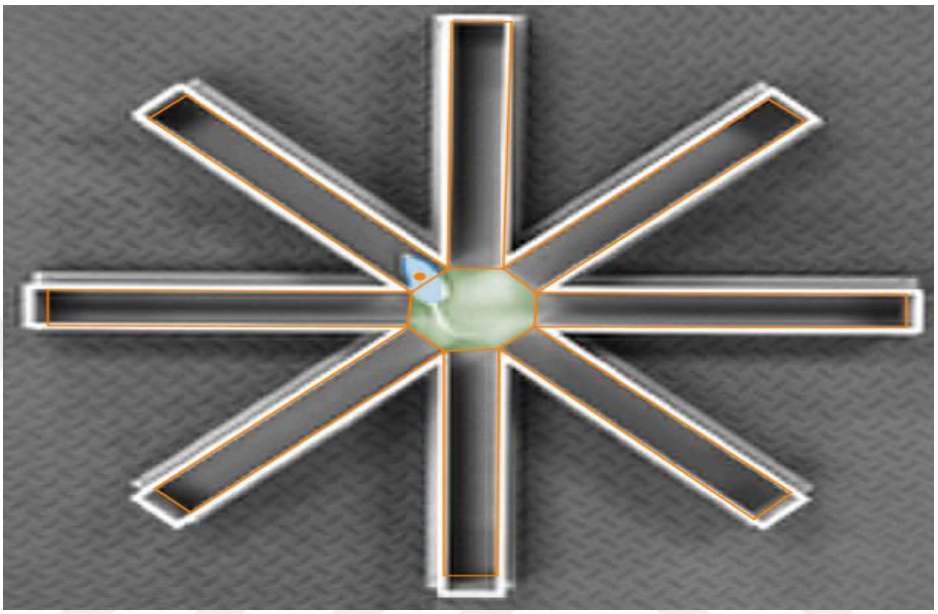


Figure 7. Radial arm-maze test apparatus

2.2.4.Elevated plus-maze test (EPM)

Behaviour in EPM is also utilized to evaluate exploration, anxiety, and motor behaviour. The EPM compose of four arms, each one is 49 cm long and 10 cm wide, and elevated 50 cm above the ground. Two arms were enclosed by walls 30 cm high and the two other arms were exposed. 15 min after the inhalation of *Achillea biebersteinii* volatile oil (AEO1% and AEO3%), each rat was put in the centre of the maze facing a closed arm. Behaviour was noticed for 5 minutes, and the time spent and a number of entries into the open and enclosed arms was calculated (Hayashi et al., 2012). The percentages of time spent in the open arms (time spent in the open arms / time spent in all arms x 100) were counted. furthermore, the total number of open and enclosed-arm entries (number of crossing), which indicates the exploratory activity of animals (Rodgers and Dalvi, 1997). Were measured. An entry was defined as an animal placing all of the limbs into an arm, when the animal was in the central area, the time wasn't recorded.

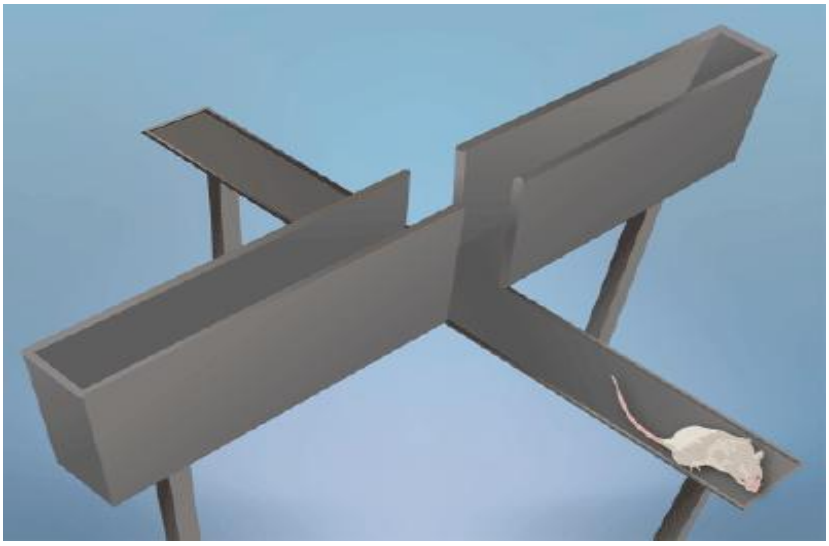


Figure 8. Elevated plus-maze test apparatus

2.2.5.Forced swimming test (FST)

The FST is the most commonly used model for evaluating depressive-like response (Cryan et al., 2002). The depressive-like response was evaluated, essentially using the same process defined by Campos, Fernandes (Campos et al., 2005). But with alteration. On the first day of the test, rats were individually placed into cylindrical recipients (diameter 30 cm, height 59 cm) containing 25 cm of water at 26 ± 1°C. The animals were left to swim for 15 minutes before being removed, dried and turned back to their cages. The procedure was repeated after 24 hours, in a 6 min swim session, 15 min after the inhalation of *Achillea biebersteinii* volatile oil (AEO1% and AEO3%). During the test session, the next behavioural responses were recorded: (1) immobility (time spent floating with the minimal movements to keep the head above the water); and (2) swimming (time spent with active swimming movements).

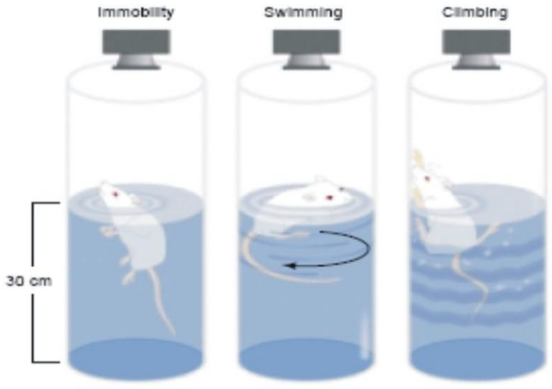


Figure 9. Forced swimming test

2.2.6. Biochemical Parameter Assay

2.2.6.1. Determination of Amygdala and Hippocampal SOD Activity

Elisa kit for rat tissues by Rel Assay was used to determine SOD activity. The protocol was followed according to the kit. Briefly, standarts of the kit and the samples were feed in each well and then we feed 50µl working solution of biotinylated antigen. Then the plate was incubated in 37 °C, for 60 minute . Then the plate was washed with washing buffer 5 times. 50 µl avidin-HRP was feed and the plate was incubated again for 60 minute. The plate was washed with washing buffer. Substrate A and B were feed and then stop solution was added to stop the reaction. The plate was measured under 450 nm wavelength.

2.2.6.2. Determination of Amygdala and Hippocampal GPX Activity

Elisa kit for rat tissues by Rel Assay was used to determine GPX activity. The protocol was followed according to the kit. Briefly, standarts of the kit and the samples were feed in each well and then we feed 50µl working solution of biotinylated antigen. Then the plate was incubated in 37 °C, for 60 minute . Then the plate was washed with washing buffer 5 times. 50 µl avidin-HRP was feed and the plate was incubated again for 60 minute. The plate was washed with washing buffer. Substrate A and B were feed and then stop solution was added to stop the reaction. The plate was measured under 450 nm wavelength.

2.2.6.3.Determination of Amygdala and Hippocampal Content of Reduced GSH

Elisa kit for rat tissues by Rel Assay was used to determine content of reduced GSH activity. The protocol was followed according to the kit. Briefly, standarts of the kit and the samples were feed in each well and then we feed 50µl working solution of biotinylated antigen. Then the plate was incubated in 37 °C, for 60 minute . Then the plate was washed with washing buffer 5 times. 50 µl avidin-HRP was feed and the plate was incubated again for 60 minute. The plate was washed with washing buffer. Substrate A and B were feed and then stop solution was added to stop the reaction. The plate was measured under 450 nm wavelength.

2.2.6.4.Determination of Amygdala and Hippocampal MDA Level

Elisa kit for rat tissues by Rel Assay was used to determine MDA level. The protocol was followed according to the kit. Briefly, standarts of the kit and the samples were feed in each well and then we feed 50µl working solution of biotinylated antigen. Then the plate was incubated in 37 °C, for 60 minute . Then the plate was washed with washing buffer 5 times. 50 µl avidin-HRP was feed and the plate was incubated again for 60 minute. The plate was washed with washing buffer. Substrate A and B were feed and then stop solution was added to stop the reaction. The plate was measured under 450 nm wavelength.

2.3.Statistical analysis

Behavioural scores within Y-maze, radial arm maze, elevated plus-maze and forced swimming tasks were analysed by one- way (ANOVA) followed by Tukey post hoc test using GraphPad Prism 7 software for Windows. To assess differences between groups in the radial arm maze test, separate repeated-measures ANOVA were calculated on the number of working memory errors and the number of reference memory errors with the group (Control, Sco.alone, Sco+ AEO1% and AEO3%), as between-subject factor and days (1 - 7) as within-subjects factors. All consequences are expressed as mean ± standard error of mean (S.E.M). F values for which ($p<0.05$) were considered as statistically significant. Pearson's correlation coefficient and regression analysis were used so as to estimate the relationship between behavioural measures.

3. RESULTS

3.1. Chemical Composition of the *A. bieberstenii* Volatile Oil

The GC-MS/GC-FID investigation of the volatile profiles in *A. biebersteinii* volatile oil is recorded in Table 1. An aggregate of 53 unique blends was isolated which compose 98.9% (w/w) of the aggregate volatile oil. As a consequence of GC-MC examination, eucalyptol 33.2 % was the major compound in the sample studied. Furthermore, other major compounds were camphor 11.4 %, 2-Isopropyl-5-methyl-3-cyclohexen-1-one 10.4%, Eugenol 6.2 %, α- Terpineol 5.0%, o-Cymol 4.7 % , which accounted for 33% of the total essential oil.

Table 1. Chemical composition of the Volatile oil of *A. biebersteinii*

Chemical Composition of the volatile oil of *A. bieberstenii*			
NO	Compounds	RI	Concentration (%)
1	2-Hexanal	964	0.1
2	Santolina triene	996	0.1
3	Tricyclene	1010	0.1
4	α- Thujene	1020	0.5
5	α- Pinene	1020	**2.9**
6	Camphene	1030	**2.1**
7	Sabinene	1050	1.6
8	β-Pinene	1055	1.8
9	α- Phellandrene	1077	0.1
10	α- Terpinene	1081	0.3
11	**o-Cymol**	1090	**4.7**
12	**Eucalyptol**	**1100**	**33.2**
13	γ -Terpinene	1118	0.5
14	Trans-Sabinene hydrate	1126	0.3
15	α- Terpinolene	1137	0.1
16	cis-Sabinene hydrate	1149	0.3
17	Chrysanthenone	1160	0.4
18	trans-2-Menthenol	1167	**2.1**
19	Trans-pinocarveol	1180	0.3
20	1-terpinol	1180	1.4
21	**Camphor**	1184	**11.4**

22	Sabina ketone	1189	1.0
23	Borneol	1200	1.9
24	4-Terpineol	1205	1.6
25	α- Terpineol	1216	**5.0**
26	Trans-piperitol	1224	0.9
27	Trans-carveol	1231	0.3
28	phenylpropionaldehyde	1248	0.3
29	**2-Isopropyl-5-methyl-3-cyclohexen-1-one**	1260	**10.4**
30	phellandral	1280	0.1
31	(-) Borneol acetate	1280	1.9
32	Cuminol	1289	0.8
33	Perillol	1295	0.2
34	1.4 p-Menthadien 7-ol	1321	0.4
35	**Eugenol**	1339	**6.2**
36	Cis-jasmone	1371	0.2
37	Trans-caryophyllene	1391	0.1
38	Germacrene D	1434	0.6
39	β-Selinene	1439	0.1
40	Bicyclogermacrene	1443	0.1
41	1,5 epoxysalvial 4(14) ene	1488	0.1
42	(-) Spathulenol	1494	0.2
43	Caryophyllene oxide	1497	0.4
44	(-) β-cadinene	1525	0.2
45	β-Eudesmol	1538	0.4
46	Tetradecanoic acid	1590	0.1
47	Hexahydrofarmesyl acetone	1630	0.1
48	1-heptadecanol	1648	0.1
49	n-hexadecanoic acid	1692	0.3
50	Phytol	1791	0.1
51	Linoleic acid	1810	0.1
52	Tricosane	1900	0.1
53	nonacosane	1932	0.3
	TOTAL		**98.9**

RI: experimental Retention indices relative to n-alkanes on the HP-5 MS column.

3.2. Impact of the *A. biebersteinii* Volatile Oil on Spatial Memory in Y-Maze Test

The one-way ANOVA detected significant overall differences between all groups [f (3, 16) = 5.55, (P < 0.001)] on spatial working memory, as manifested by the

spontaneous alternations percentage as shown in (Figure 10A). Also, the Tukey's post hoc analysis detected significant differences between control versus Sco-alone treated group ($p < 0.01$) and Scopolamine-alone treated group vs Sco+AEO3% groups ($p<0.001$) for the spontaneous alternations percentage (Figure 10A). The adjustments in the spontaneous alternation percentage of sco-treated rats exposed to *A. biebersteinii* volatile oil is not associated with the changes in motor action, as proved by the number of arm entries compared to scopolamine alone treated rats. Tukey's post hoc analysis revealed significant differences between all groups [f (3,12) =5.19, ($p < 0.01$)] on the number of arm entries as shown in (Figure 10B).

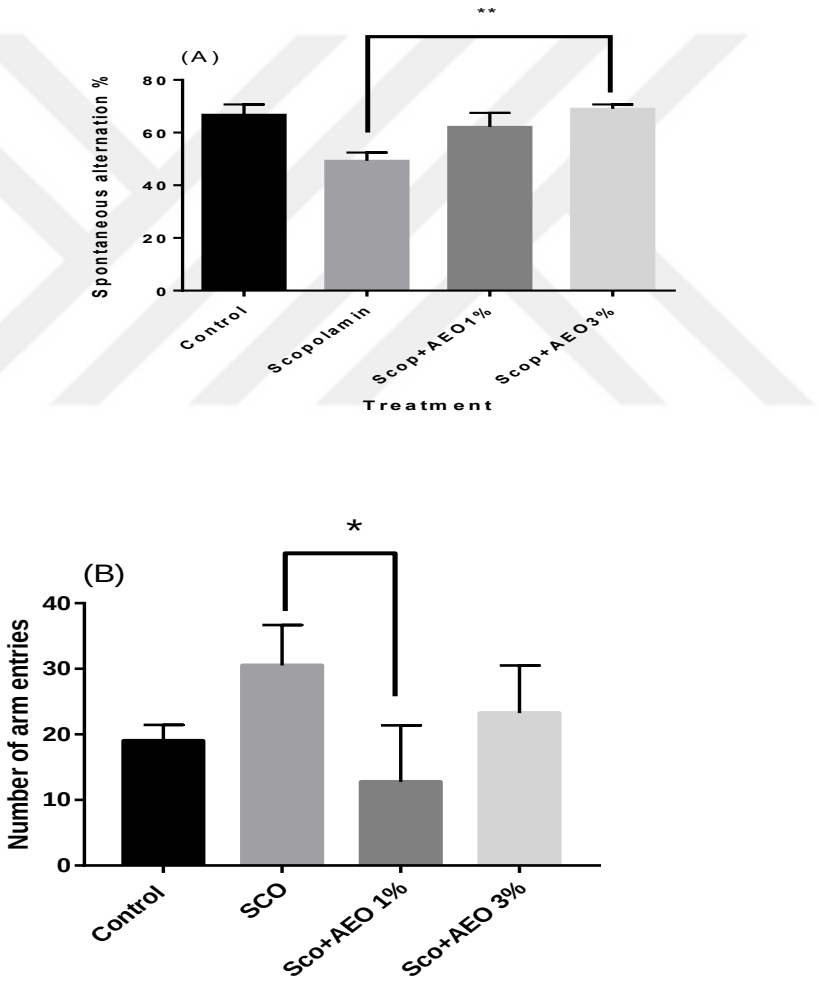
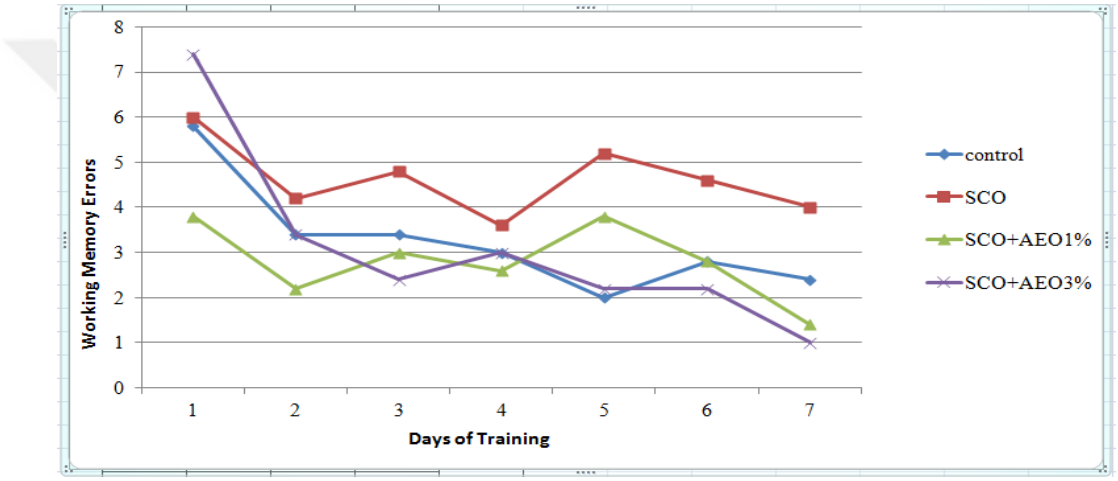


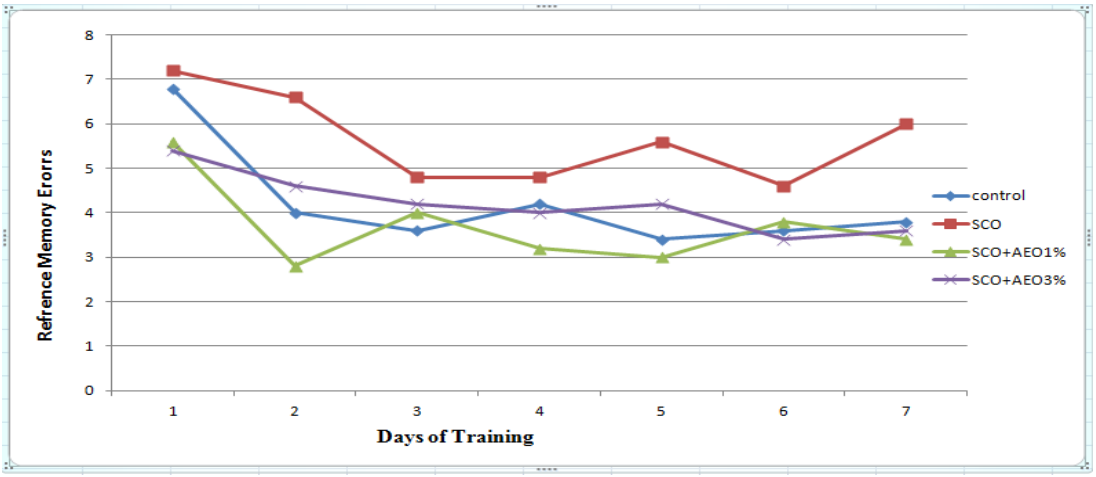
Figure 10. Impact of inhaled *A. biebersteinii* volatile oil (AEO1% and AEO3%) in the Y-maze on spontaneous alternation % (A) and the number of arm entries (B) in the (Sco)-alone treated rats. values are mean ± S.E.M. (n = 7 animals per group), *P < 0.01 **P < 0.001.

3.3. Impact of the *A. biebersteinii* Volatile Oil on Spatial Memory in Radial Arm-Maze Test .

To explore whether inhalation of the *A. biebersteinii* volatile oil in scopolamine-treated rats impacts spatial memory, the rats were further assessed in the radial arm maze test. For working memory errors, one-way ANOVA detected a significant time difference [$F(6.112) = 7.95$, ($p < 0.0001$)] and a significant group difference [$F(3,112)=4.415$, ($p < 0.005$)] as shown in (Figure 11A). For reference memory errors, one-way ANOVA did not reveal any statistically differences between groups and time as shown in (Figure 11B).



(A)



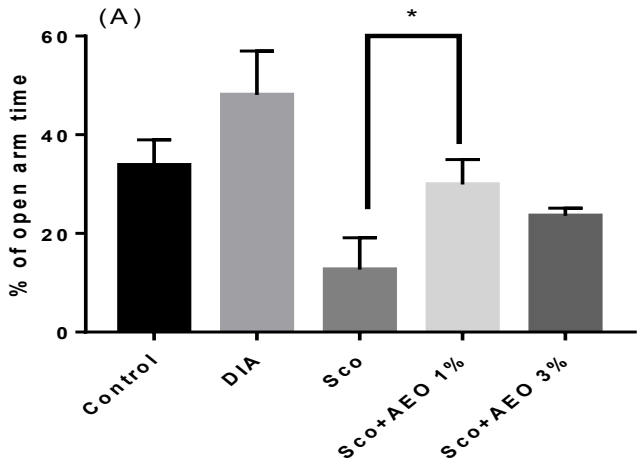
(B)

Figure 11. Impact of the inhaled *A. biebersteinii* volatile oil (AEO1% and AEO3%) on the working memory errors (A) and the reference memory errors (B) during 7 days training in the radial arm-maze in the (Sco)-alone treated rats. values are means±SEM (n =7 animals per group).

3.4. Impact of the *A. biebersteinii* Volatile Oil on Elevated Plus Maze Test.

The one-way ANOVA, detected a significant overall distinction between all groups [F (4, 15) = 4.88, ($p < 0.01$)] on the percentage of the time spent in the open arms (Figure 12A). Moreover, Tukey's post hoc analysis detected a significant difference between Sco. versus Sco+AEO1% ($p < 0.05$), the DIAZ vs the Scopolamine groups ($p < 0.005$), on the percentage of the time spent in the open arms (Figure 12A). Also,one way ANOVA detected a significant overall distinction between all groups [$F(4,15)=5.13$,($p < 0.01$)] on the number of open-arm entries (figure 12B). Tukey's post hoc analysis detected a significant difference between Sco. versus Sco+AEO1% ($p < 0.01$), the diazepam versus the Sco.groups ($p < 0.01$), on the percentage of the time spent in the open arms. Additionally,one-way ANOVA show a significant overall difference between all groups [$F(4,15)=10.78$, ($p <0.0001$)] on the number of crossing. Moreover, Tukey's post hoc analysis detected a significant difference between the control versus the Sco-alone treated group ($P < 0.01$), the diazepam versus the Sco.alone treated group ($P<0.001$), the scopolamine alone treated group versus Sco+AEO1% ($P < 0.001$), the Sco-alone treated group versus Sco+AEO3% groups ($P <0.0001$), for the number of crossing as shown in (Figure 12C).

The diazepam injection, as the positive standard, significantly increases the percentage of the time spent in the open arms, the number of open-arm entries, and the number of crossing, produce significant anxiolytic effects.



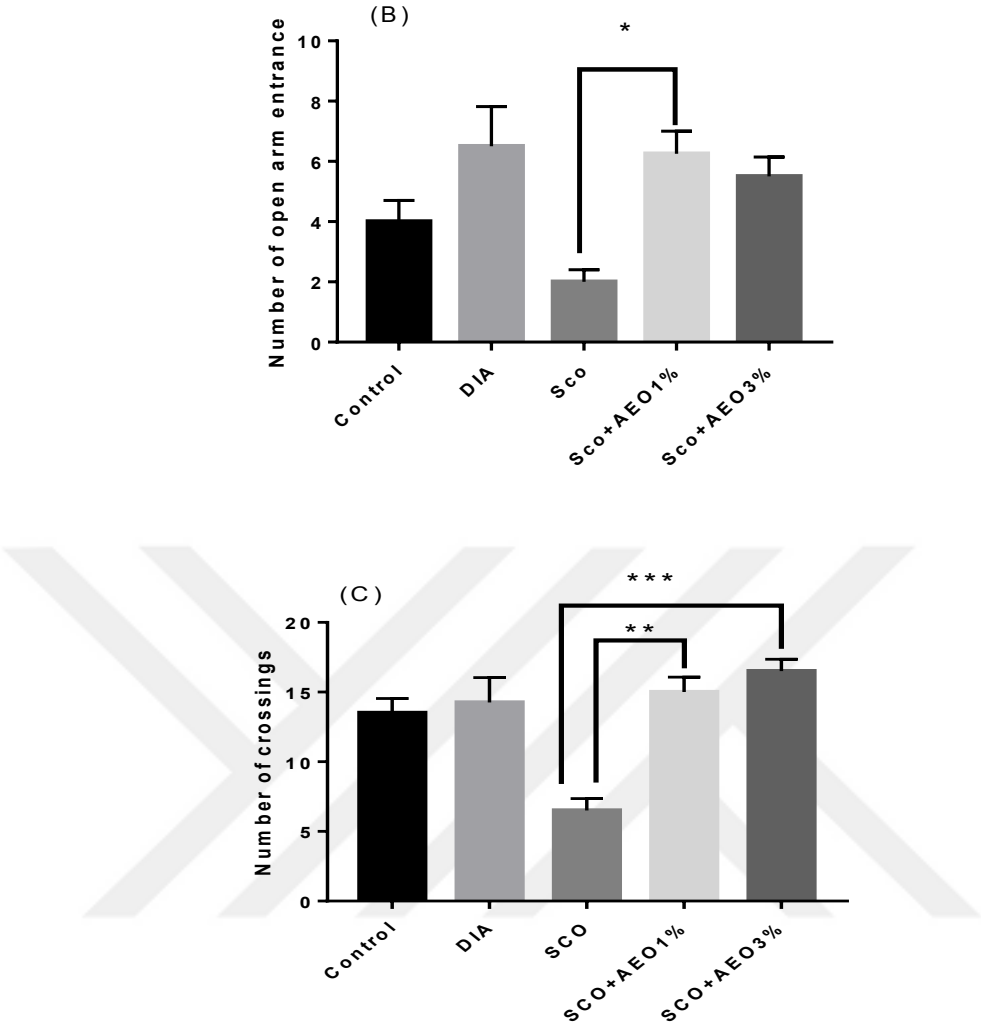


Figure 12. Impacts of the inhaled in *A. biebersteinii* volatile oil (AEO1% and AEO3%) in the elevated plus-maze test on the percentage of the time spent in the open arms (A), the number of open-arm entries (B), and number of crossing (C) in the (Sco)-alone treated rats. Values are means±SEM (n=7 animals per group). * p < 0.01,**P < 0.001,***P < 0.0001

3.5. Impact of the *A. biebersteinii* Volatile Oil in the Rat Forced Swimming Test

In the FST, ANOVA detected a significant overall distinction between all groups in the swimming time [F(4,15)=34.37, (p < 0.0001)] as shown in (Figure 13A). Also, on the immobility time [F(4,15) = 41.26, (p < 0.0001)] as shown in (Figure 13B). Moreover, Tukey's post hoc analysis detected a significant distinction between the control versus the Scopolamine alone treated groups (P < 0.001), the control vs. the Sco+AEO3% groups (P < 0.01), the tramadol versus the Scopolamine alone treated group (P<0.0001), the Scopolamine alone treated group versus the Sco+AEO1% groups (P<0.0001), the

Scopolamin alone treated group versus the Sco+AEO3% groups (P < 0.0001), for the swimming time, as shown in (Figure 13A). Also, Tukey's post hoc analysis detected a significant difference between the control versus the Sco+AEO1% groups (P<0.0001), and the control versus the Sco+AEO3% groups (P < 0.0001). The tramadol versus the Sco. alone treated groups (P < 0.0001), the Sco. alone treated groups versus the Sco+AEO1% groups (P <0.0001), the Sco. alone treated group versus the Sco+AEO3% groups (P < 0.0001) for the immobility time as shown in (Figure 13B).

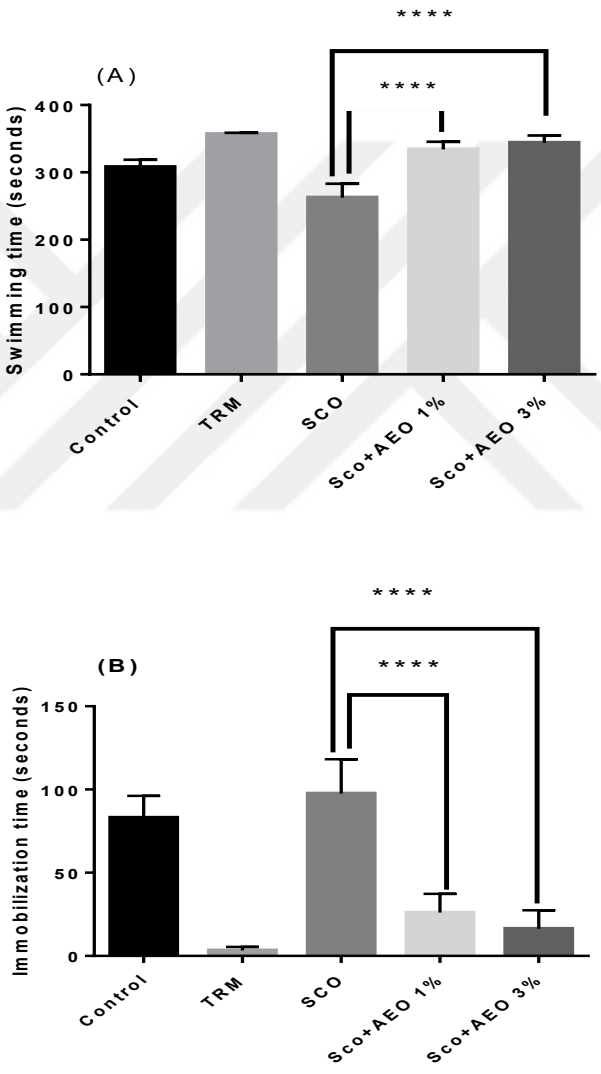
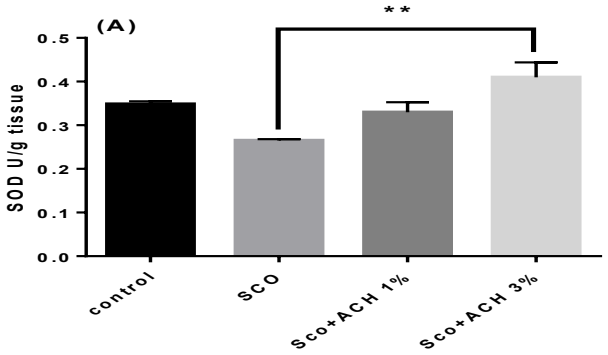
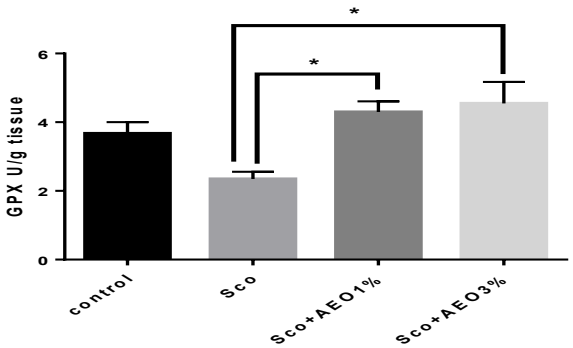


Figure 13. Impacts of the inhaled in *A. biebersteinii* volatile oil (AEO1% and AEO3%) on swimming time (A) and immobility time (B) in the Scopolamine-alone treated groups during the six minutes. Values are means ± SEM (n=7 animals per group). ****P < 0.0001

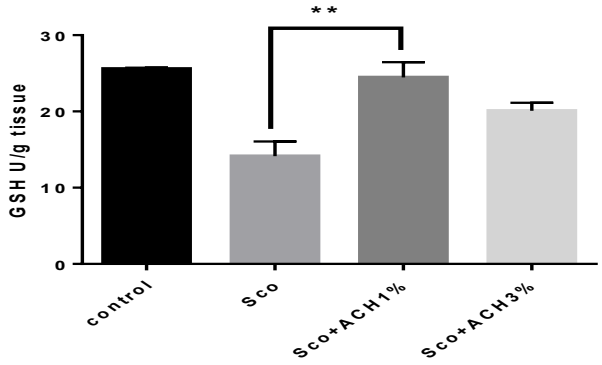
3.6. Impact of the *A. biebersteinii* Volatile Oil on SOD, GPX Activities and Total Content of Reduced GSH and MDA levels in the Rat Amygdala Homogenates.

For SOD and GPX specific activities along with reduced GSH and MDA level evaluated in the rat amygdala homogenates, ANOVA detected significant overall differences between all groups for SOD [F (3, 8) = 8.07, (P < 0.001)] as shown in (Figure 14A), GPX [F (3,8) = 6.05, (P < 0.01)] as shown in (figure 9B), GSH [F (3, 8) = 12,18, (P < 0.001)] as shown in (Figure 14C), and MDA [F(3, 8) = 22,59, (P < 0.0001)] as shown in (Figure 14D). Also, Tukey's post hoc analysis revealed significant differences between the scopolamine alone treated group versus Sco+AEO3% (P<0.005), for SOD specific activities (figure 14A). Scopolamine alone treated group versus Sco+AEO1% (P < 0.01), Sco-alone treated group versus Sco+AEO3% (p<0.01) for GPX specific activities (Figure 14B). Significant differences between the control versus scopolamine alone treated group (P<0.001),the sopolamine alone treated group versus the Sco+AEO1% (P < 0,005) for the total content of reduced GSH as shown in (Figure 14C). Significant differences between Sco-alone treated group versus Sco+AEO1% (P < 0.0001), and Sco- alone treated group versus Sco+AEO3% (P < 0.001) were detected for the total content of reduced MDA (Figure 14D).

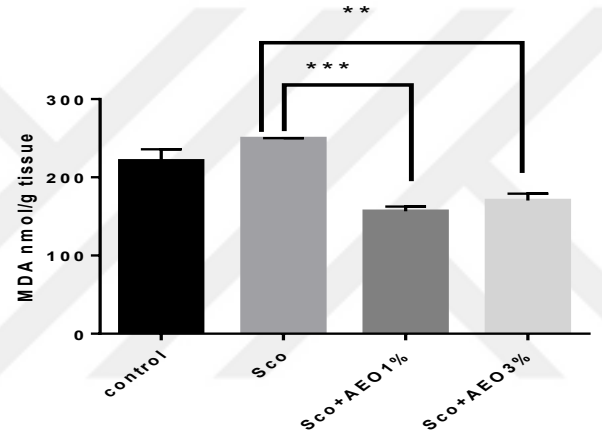




(B)



(C)



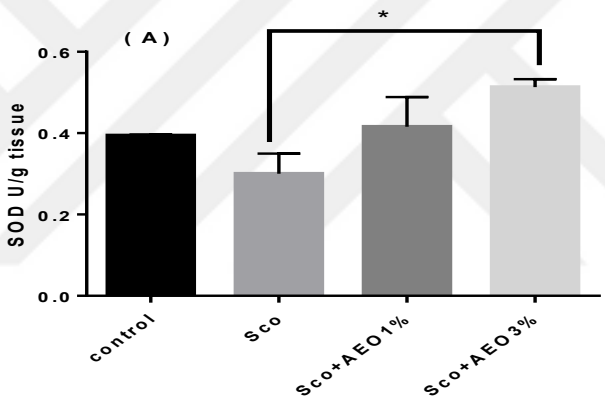
(D)

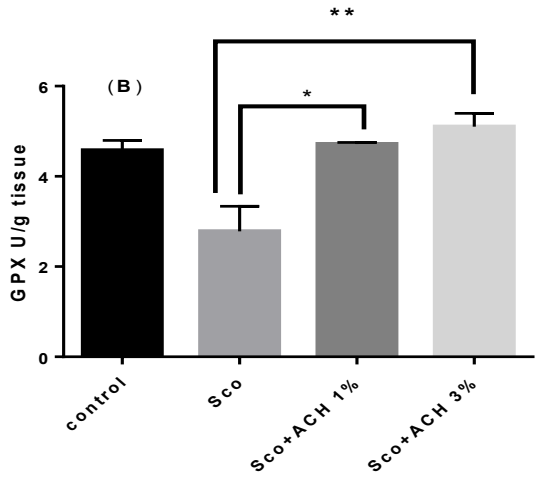
Figure 14. Impact inhaled of the *A. biebersteinii* volatile oil (AEO1% and AEO3%) in rat amygdala homogenates on SOD (A),GPX(B) specific activities, on reduced GSH(C), and MDA(D) levels in the scopolamine (Sco) alone -treated rats. Values are the means ± SEM (n = 7 animals per group). For Turkey's post-hoc analyses *P < 0.01 and **P < 0.001,***P < 0.0001

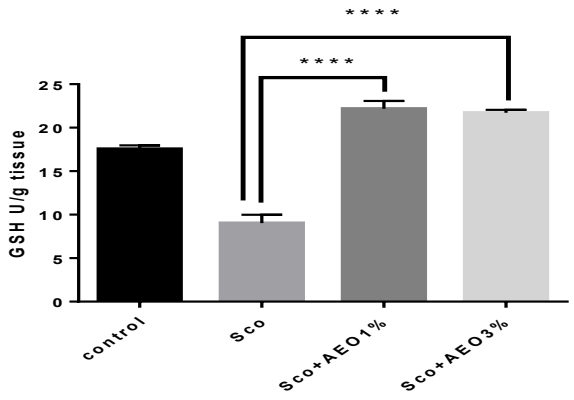
3.7. Impact of the *A. biebersteinii* Volatile Oil on SOD, GPX Activities and Total Content of Reduced GSH and MDA levels in the Rat Hippocampal Homogenates.

For SOD and GPX specific activities along with reduced GSH and MDA levels evaluated in the rat hippocampal homogenates, ANOVA detected significant overall differences between all groups for SOD [F (3, 8) = 3.74 , (P< 0.05)] as shown in (figure 15A), GPX [F (3, 8) = 9.58 , (P< 0.005)] as shown in (Figure 15B). for GSH [F (3, 8) = 73,48) , (P < 0.0001)] as shown in (Figure 15C), and MDA [F (3, 8) = 9.38, (P < 0.005)] as shown in (Figure 15D). Also, Tukey's post hoc analysis revealed significant differences between the scopolamine alone treated grous versus Sco+AEO3% (P < 0.05), for SOD

specific activities (Figure 15A). Significant distinction between the control versus scopolamine alone treated group (P < 0.01), The scopolamine alone treated group versus the Sco+AEO1% (P < 0.01), The scopolamine alone treated group versus the Sco+AEO3% (p < 0,005) For GPX specific activities as shown in (Figure 15B). Significant distinction between the control versus scopolamine alone treated groups (P<0.0001), The sopolamine alone treated groups versus the Sco+AEO1% (P< 0,00001), The scopolamine alone treated group versus the Sco+AEO3% (P<0,00001) for the total content of reduced GSH as shown in (Figure 15C). Scopolamine alone treated group versus Sco+AEO1% (P < 0.01), scopolamine (Sco) alone treated group versus Sco+AEO3% (P < 0.005) for the total content of reduced MDA as shown in (Figure 15D).







(C)

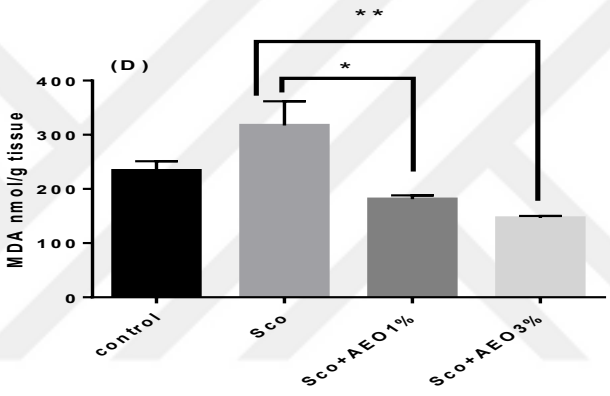


Figure 15. Impact inhaled of the *A. biebersteinii* volatile oil (AEO1% and AEO3%) in the rat hippocampal homogenates on SOD (A),GPX (B) specific activities, on reduced GSH (C) and MDA (D) levels in the scopolamine (Sco) alone -treated rats. Values are the means ± SEM (n = 7 animals per group). For Turkey's post-hoc analyses *P < 0.05, ** p < 0.005,****P < 0.00001.

4. DISCUSSION

In the present research, we studied whether inhalation of the *Achillea biebersteinii* essential oil (AEO 1% and AEO 3 %) effects on spatial memory performances in the scopolamine model of Alzheimers disease. After inhaling of the essential oil for 21 continuous days in rats subjected to intraperitoneal injection of scopolamine, formed memory impairment, as declared in the previous studies (Hsieh et al., 2003; Ngoc et al., 2014; Lee et al., 2014; Hritcu et al., 2015a). We used different behavioural tests in this study; Y-maze, Radial arm maze, elevated plus maze and forced swimming test to the evaluation of the behavioral test of the animal models. These tasks can test hippocampus-subordinate short-term, long -term and spatial memory formation, which are especially influenced by Alzheimer's disease (Hritcu et al., 2015b). Our consequences plainly exhibited that inhalation of *Achillea biebersteinii* essential oil maintains spatial memory processing in a rodent model of scopolamine induced learning and memory weakens. This result also reported that in some studies by using different plants essential oils like *Pimpinella peregrine* (Aydin et al., 2015), *Ferulago angulata* (Bagci et al., 2015), lavender oil (Hritcu et al., 2012).

The chromatographic analysis of the essential oils detected that the major volatile oil components of *A. biebersteinii* oil are eucalyptol (33.2%), camphor (11.4%) and eugenol (6.2%). Prior reports indicated that the eucalyptol have a defensive influence of on aggravation and gives extra confirmation to its potential gainful use in treatment as an anti-inflammatory factor in neurodegenerative disease (Khan et al., 2014). Eucalyptol (1,8-cineole), a terpenoid oxide separate from *Achillea biebersteinii*, is a promising compound for treating such conditions such as neurodegenerative disease (Seol and Kim, 2016). Also other components of *Achillea biebersteinii*, 2-Isopropyl-5-methyl-3-cyclohexen-1-one (10.4%), Eugenol (6.2%), α-Terpineol (5.0%), o-Cymol (4.7%), α- Pinene (2.9%) were found as the main components. The common properties of these components incorporate anticonvulsant, narcotic properties, carminative, aromatic, antispasmodic, anti-depressant, antimicrobial, astringent, stimulatory activities and anxiety relieve (Sayorwan et al., 2013; Mesfin et al., 2014).

The Y-maze task is a behavioural test which assessed the willingness of rats to investigate the new place. Rats normally like to examine another arm of the maze rather than coming back to one that was already visited. In the spontaneous alternation test, a few sections of the brain as the hippocampus, septum, basal forebrain, and prefrontal cortex are included (Foyet et al., 2015). The high dose of *A. biebersteinii* volatile oil in scopolamine-treated rats altogether enhanced spatial working memory in the Y-maze test as shown in (Figure 10A). As evidenced by the rise of spontaneous alternation rate when compared with scopolamine alone treated rats. This consequences proposes that the high dose of *A. biebersteinii* volatile oil (AEO3 %) utilized as a part of this study shows an enhanced impact on obtaining of the short-term memory of scopolamine-treated rats inside the Y-maze test. The improvement of spatial working memory inside Y-maze task can't be ascribed to locomotor activity, because a significant alteration in the number of entries of the groups treated with the *A. biebersteinii* volatile oil as compared with scopolamine alone treated groups were recognized as shown in (Figure 10B).

Radial arm maze task is widely utilized to examine spatial memory (Foyet et al., 2015). These Radial arms maze analysis are important in assessing the impact of medications, anxiety and different other environmental factors on learning and memory (Cioanca et al., 2013). When scopolamine treated rats exposed to AEO1% and AEO3% display an improvement of working memory as shown in (Figure 11A), when compared to scopolamine alone treated groups, for seven days training in the radial arm maze test. Then again, both doses of inhaled in *A.biebersteinii* volatile oil (AEO1 and AEO3 %) non-significantly enhanced long-term memory of scopolamine-treated rats, investigated by reference memory inside the radial arm maze test as shown in Figure 11B. In addition, time is taken to devour every one of the 5 baits was more significantly enhanced after scopolamine-treated rats were treated with high dose of AEO.These investigations could indicated that *A.biebersteinii* essential oil performs an important role in spatial memory formation, particularly on working memory. Beside, non-significant difference statistically were seen between groups and time on reference memory in the radial arm maze task. Working memory and reference memory are the two factors that report the physiological status of the brain (Cioanca et al., 2013).

The elevated plus-maze is recognized as a valuable model able to predict anxiolytic- or anxiogenic-like effects of drugs (Aydin et al., 2015). Anxiety and depression are frequently in Alzheimer's disease case and is associated with period of dementia, large seriousness of dementia and lower instruction levels (Cioanca et al., 2014). As shown in (Figure 12A,B and C). Sco-alone treated rats have diminished the percentage of the time spent in the open arms, the number of open-arm entries and the number of crossing in the elevated plus-maze task. This mean that the sco-alone treated rats experienced large amounts of anxiety and were suitable for assessing the presumed anxiolytic substances as our volatile oil (Aydin et al., 2015). The inhalation of *A.biebersteinii* volatile oil in Sco-treated rats produces anxiolytic-like activity. Besides, after the sco-treated rats being exposed to *A.biebersteinii* essential oil, the percentage of time spent in the open arms significantly rised, particularly in the group exposed to (AEO1 %) compared to Sco-alone treated group. Also, the number of open arms entries increased, particularly in the group of scopolamine-treated rats exposed to *A.biebersteinii* essential oil (AEO1 %) when compared with scopolamine-alone treated group. Additionally, the number of crossing increased significantly when exposed to both doses of *A.biebersteinii* (AEO1% and AEO3%) particularly in the group exposed to (AEO3%), when compared with scopolamine alone treated group. Also significant differences were noticed between both doses of *A.biebersteinii* volatile oil (AEO1% and AEO3%) on the number of crossing.

Obviously, diazepam as a benzodiazepine medication utilized as positive control formed significant increases in the percentage of time spent in the open arms, the number of open arm entries, and the number of crossing when compared with scopolamine-alone treated group. These data are consistent with the results of numerous previous studies, which have shown that DZP and other benzodiazepines produce significant anxiolytic effects in a variety of anxiolytic screening procedures, including elevated plus-maze test procedures (Aydin et al., 2015). The pharmacological action of diazepam enhances the effect of the neurotransmitter GABA by binding to the benzodiazepine site on the GABAA receptor (via the constituent chlorine atom) leading to central nervous system (CNS) depression. The anxiolytic impact of diazepam has as of late been shown to be mediated by α 2 $GABA_A$ receptors, which are found mostly in limbic regions, As diazepam expands

the action of GABA in the brain, it produce the sedative impact (Florence Crestani et al., 2001). In accordance with already published paper, diazepam increased the percentage of open arm entries and the time spent in the open arms (Emamghoreishi et al., 2005). In accordance with data of these study, Eucalyptol (33.2%) and other some components that is including in *A.biebersteinii* volatile oil have increased the anxiolytic-like behaviour and anti-depressive-like response in scopolamine-treated group.

The forced swimming task has been validated as a suitable tool to test the antidepressant properties of medications (Cioanca et al., 2014). When rats are forced to swim in a limited space, after an initial time of struggling, they would get to be stable, looking like a condition of gloom and mental despair. This unpreventable stressful condition can be assessed by evaluating different behavioural approach (Tolardo et al., 2010; Cioanca et al., 2014; Aydin et al., 2015). As shown in (Figure 13A and B), in sco- alone treated rats the swimming time reduced and the immobility time increased as compared to control rats. Subsequent to being exposed to both doses of *A.biebersteinii* volatile oil (AEO1% and AEO3%) increased significantly the swimming time in both groups exposed to (AEO1% and AEO3%) as compared to scopolamine alone treated group. Additionally, the reduce of the immobility time, in both groups after exposed to (AEO1% and AEO3%) volatile oil when compared with sco-alone treated rats, was also observed.

These investigations indicate that the *A.biebersteinii* volatile oil has a potent an antidepressant-like response to an inescapable anxiety. In our research, tramadol, used as a positive control, produced significant increases in the swimming time and reduce the immobility time as compared with scopolamine-alone treated rats. Accordance with previous study, tramadol is a single drug with multiple modes of activity. Besides its central impacts on mu receptors, at the peripheral level, tramadol inhibits serotonin and norepinephrine reuptake. It is an analgesic and it is additionally considered as an antidepressant (Sansone and Sansone., 2009 ; Aydin et al., 2015). The CNS is very susceptible to oxidative stress as the brain has a high consumption of oxygen, includes large amounts of free-radical generating iron and substances such as ascorbate, glutamate and polyunsaturated fatty acids, that easily undergo redox-reaction cause to lead the radicals' formation and presents relatively

poor antioxidant defense systems (Bagci et al., 2015). Furthermore, the recent researches indicated that free radicals are involved in the pathogenesis, leading to the oxidative destruction of DAN neurons in the substantia nigra (Ciobica et al., 2012). Previously it has been reported that scopolamine is related with elevated oxidative stress in the entire brain, Also in special structures correlate with memory and learning (Deep et al., 2012).

Also the present research, estimated whether memory impairment induced by scopolamine is connected with altered oxidative stress indices. Scopolamine alone treated rats had decreased superoxide dismutase (SOD) as shown in Figure 14A,15A and glutathione peroxidase (GPX) specific activities as shown in (Figure 14B,15B), with decreased the total content of glutathione (GSH) as shown in (Figure 14C,15C) and increasing malondialdehyde (MDA) as shown in (Figure 14D,15D) levels within the rat amygdala and hippocampal homogenates respectively. Additionally, we noticed a significant reduction in SOD, GPX specific activities and the total content of decreased GSH along with elevated MDA levels in the rat amygdala and hippocampal homogenates of the scopolamine alone treated group. The reduces of the SOD and GPX specific activities showed to parallel elevated in the MDA levels in the rat hippocampal and amygdala homogenates indicating that these events are required to scavenge superoxide radicals induced by scopolamine. MDA is the most abundant individual aldehyde resulting from lipid peroxidation and can be considered a marker of lipid peroxidation (Hritcu et al., 2014). Our results confirm the hypothesis that reduces SOD activity can lead to an accumulation of H2O2. With a lack of a simultaneous increase in GPX activity, this could enhance the stimulation of lipid peroxidation and protein oxidation, at the end causing cellular destruction (Hritcu et al., 2011). After scopolamine treated groups exposed to essential oil (AEO1% and AEO3%), was able to overwhelm the pro-oxidant effects of scopolamine in the rat amygdala and hippocampus homogenates evidenced by an increase in antioxidant enzymes activities (SOD and GPX) and the total content of reduced GSH and the decrease of MDA levels. This consequences indicate that the *A.biebersteinii* volatile oil have strong antioxidant activity by scavenging reactive oxygen species and using a protective effect against oxidative stress induced by scopolamine.

This information indicated that memory increase scores with-in Y-maze

and radial arm maze test alongside reduction of stress and depressive-like behaviours inside elevated plus-maze and forced swimming tests could be associated with the involvement of the inhaled in *A.biebersteinii* volatile oil against scopolamine induced memory weakness, anxiety and depression in lab rats. Also our results suggests that *A.biebersteinii* essential oil (AEO1% and AEO3%), was able to overcome the pro- oxidant effects of scopolamine in the rat amygdala and hippocampal homogenates evidenced by an increase in antioxidant enzymes activities (SOD and GPX) and the total content of reduced GSH and the decreased of MDA level.

5. CONCLUSIONS

In brief, our investigation proposes that *A. biebersteinii* essential oil increase memory-enhancing, anxiolytic and antidepressant effects in sco-alone treated rats. In results, inhalation of the *A. biebersteinii* volatile oil may produce useful alternative or complementary choice in either the protecting or the treatment of neurodegenerative dysfunction close associated with Alzheimer's disease disorder.

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