

**REPUBLIC OF TURKEY
FIRAT UNIVERSITY
GRADUATE SCHOOL OF NATURAL AND
APPLIED SCIENCE**



**THE NEUROPROTECTIVE EFFECTS OF INHALED
JUNIPERUS OXYCEDRUS L. SUBSP. *OXYCEDRUS* ESSENTIAL
OIL ON SCOPOLAMINE-INDUCED ALZHEIMER'S TYPE
DEMENTIA**

MASTER THESIS

SAFEEN AHMED OTHMAN

Supervisor: Prof. Dr. Eyüp BAĞCI

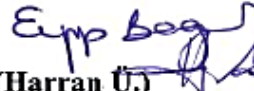
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ABSTRACT

THE NEUROPROTECTIVE EFFECTS OF INHALED *JUNIPERUS OXYCEDRUS* L. SUBSP. *OXYCEDRUS* ESSENTIAL OIL ON SCOPOLAMINE-INDUCED ALZHEIMER'S TYPE DEMENTIA

In this study, the neuroprotective effects of the essential oils from medicinal plant *Juniperus oxycedrus* L. subsp. *oxycedrus* distributed in Turkey on scopolamine induced Alzheimer's type dementia rat model were investigated. Alzheimer's disease is a neurodegenerative illness and increased more in the near future. *Juniperus oxycedrus* L. Subsp. *oxycedrus* has been used in traditional medicine for several years, especially in Anatolia. The essential oil of this plant was hydrodistilled by Clevenger Apparatus and analyzed by GC-FID-MS. system. Different concentrations (1% and 3%) of the this plant essential oil inhaled to the animals for 14 continuous days. In the essential oil, α -pinene (42.9 %) was found to be the the major component. Inhalation of this oil caused to increase spontaneous alternations % in Y-Maze tests and decreased working memory errors and reference memory errors in Radial Arm-Maze tests, increased the number of open-Arm Entries, increased open arm time percentage and number of Arm Crossings in Elevated Plus-Maze tests, increased swimming time and decreased immobility time in forced swimming test.

Key Words: Alzheimer's disease, *Juniperus oxycedrus*, essential oil, depression, memory

ÖZET

SKOPOLAMİN İLE OLUŞTURULAN ALZHEIMER TİPİ DEMANSA KARŞI *JUNIPERUS OXYCEDRUS* L. SUBSP. *OXYCEDRUS* UÇUCU YAĞI SOLUNUMUNUN SINIR-KORUYUCU ETKİLERİ

Bu çalışmada, Tıbbi bir bitki olan ve Türkiye’ de doğal yayılışı bulunan *Juniperus oxycedrus* L. subsp. *oxycedrus* uçucu yağının skopolamin ile oluşturulan Alzheimer tipi demansa karşı sinir koruyucu etkileri araştırılmıştır. *Juniperus oxycedrus* subsp. *oxycedrus* özellikle Anadolu’da yıllardan beri geleneksel tıpta kullanılmaktadır. *Juniperus oxycedrus* uçucu yağı GC-MS ile analiz edilmiştir. *Juniperus oxycedrus* essential oil % 1and *Juniperus oxycedrus* essential oil %3 grupları 14 gün boyunca uçucu yağına maruz kalmışlardır.Uçucu yağda alfa-pinen (%42.9) major bileşen olarak bulunmuştur. Uçucu yağ solunumu Y-labirentinde spontan değişim yüzdesinde artışa, radial kol labirentinde işleyen hafıza hatalarında ve referans hafıza hatalarında düşüşe, yükseltilmiş artı labirentinde açık kola giriş sayılarında, sayılarında artışa kol zaman yüzdesi ve geçiş sayılarında artışa, zorunlu yüzme testinde yüzme süresinde artışa, hareketsizlik süresinde ise düşüşe yol açmıştır.

Anahtar Kelimeler: Alzheimer hastalığı, *Juniperus oxycedrus*, uçucu yağ, depresyon, hafıza

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ABBREVIATIONS

AD	: Alzheimer's disease
APOE	: Apolipoprotein E
APOEϵ4	: Apolipoprotein E Epsilon 4
ATP	: Adenosine Triphosphate
Aβ PP	: Amyloid Beta Precursor Protein
Aβ	: Amyloid Beta
CAM	: Complementary and Alternative Medicine
CERAD	: Consortium to Establish a Registry for Alzheimer's Disease
CSF	: Cerebro-Spinal Fluid
DIA	: Diazepam
DNA	: Deoxyribonucleic Acid
FDA	: Food and Drug Administration
GABAA	: Gamma-Aminobutyric Acid
HP-tau	: Hyperphosphorylated Tau
HSV1	: Herpes Simplex Virus 1
MAPT	: Microtubule-Associated Protein Tau
MCI	: Mild Cognitive Impairment'
MMSE	: Mini-Mental State Examination
MRI	: Magnetic Resonance Imaging
mRNA	: Messenger Ribonucleic Acid
NFT	: Neurofibrillary Tangles
NMDA	: N-Methyl-D-Aspartate
PET	: Positron Emission Tomography
PHF	: Paired Helical Filaments
PSEN1 or PS1	: Presenilin 1
PSEN2 or PS2	: Presenilin 2
SP	: Senile Plaques
TRM	: Tramadol
WHO	: World Health Organization

1. INTRODUCTION

Phytotherapy is referred to plant compositions gained by extraction, fractionation, purification, scorching and concentration. These products pass into health care system either straight or after addition of extra to the energetic constituents (Eisenberg et al., 1998) (WHO, 2010). Phytotherapy have been encouraged after progressive transformation of mono drug treatment in tradional medicine in to multidrug treatment (WHO, 2010). There are many ways for acquring chemical substances, most significant ones are their existance in the nature or not. Chemicals can influence human life by a wide diversity of ways some are crucial like vitamins and mineral others are poisonous like poisons (Topliss et al., 2002). Natural original drugs play an significant role in the drug discovering process, efforts are chased for finding a lead combination for developing of synthetic drugs clinically energetic, as well as synthetic drugs also play an significant role in the process of drug discovery (Soejarto & Farnsworth , 1989).

Medicinal plant is a significant segment of indigenous therapeutic frameworks everywhere throughout the world. The ethnobotany science supplies a well off asset for regular medication innovative work (Farnsworth, 1990). "Traditional", utilization of home grown solutions uncover significant chronicled utilize, and this is unquestionably valid for some items that are accessible as "traditional herbal medicines. In many creating countries, an extensive rate of the populace relies upon traditionally experts and their armamentarium of medicinal plants in order to meet human services requires. However present day medication may exist together with such a traditional practice, herbal medicines have regularly saved their fame for chronicled and social reasons (Vishwakarma et al., 2013).Normal items have assumed a critical part through the world in treating and forestalling human disease. Regular item medications have originated from various source materials including terrestrial plants, terrestrial microorganisms, nautical living beings, and terrestrial vertebrates and spineless creatures (Newman et al., 2000) and its essentialness in current solution has been examined in various audits and reports (Jones et al., 2006). The estimation of characteristic items in such manner can be entered from:

a) The rate of presentation of new substance elements of broad constructive variety, including serving as forms for semi manufactured and through synthetic amendment.

b) The quantity of diseases treated or counteracted by these substances, and their recurrence of utilization in the treatment of disease. As of late, the utilization of traditional pharmaceutical data on plant inquire about has again gotten impressive attention (Newman & Ridge, 2007). Numerous new drugs are created by implication from plants and medicinal plants are assets of new drugs. It is around that there are more than 250,000 blossom plant species. Concentrate therapeutic plants comprehend plant poisonous quality and conserve individuals and creatures from characteristic toxins.

The ancient time ago human have been utilized medicinal plants begins as an origin of medicines. As a general rule around 20 and 125 plants are specified in the Quran and the Bible, separately, they've been utilized as medicinal terms to treat diverse diseases (Musselman, 1999). The tropical rain timberland plants are biologically and chemically unique assets as they incorporate different chemicals as safeguard operators against vermin, diseases and predators. They are a magnificent pool of medicines and chemical leads with which analysts can outline and combine new medications. Truth is told around 25% of the medications utilized as parts of present drug owe their causes to plants from tropical rainforest (Elliot, 1986). The phytochemicals can be utilized unmodified as medications, as beginning materials for the restricted combination of medications or as atomic models to incorporate new medications. More than 120 unadulterated pharmaceutical chemicals seperated from almost 100 plant species, as of late being used as medications, 40 are obtained from tropical species (Farnsworth & Soejarto, 1991). Be that as it may, less than 5% of tropical timberland plant species have been investigated for chemical combinations and medicinal values (Zakrzewski, 2002).

A large portion of tropical nations there is minimal organized research attempt to screen plants for new medications as their ability to beneficially and economically utilize these assets to their maximum capacity is constrained; rather business exercises, for example, purifying of woodlands for horticultural points and timber evacuation prevail and are rapidly harming the plant hereditary resources. In the previous five decades, therapeutic plant inquire about in Malaysia has been done for the most part by analysts from government-supported colleges and research foundations with little cooperation of enterprises and multinationals.

Plants have been utilized for the treatment of various sorts of illnesses from over 3000 years. The organically dynamic normal blends may have anticholinesterase action and can be utilized as pioneer mixes for the combination of new medications. The

bioactive substances from natural products, vegetables and therapeutic plants for the most part incorporates indole, steroidal-piperidine-alkaloids, furanocoumarins, xanthenes, flavonoids and diterpenes imitatives assume a primary part in the diminishing of numerous pathogenesis and neurodegenerative issue, for example, Alzheimer's diseases (Houghton et al., 2005; Rehman et al., 2006; Wszelaki et al., 2010). In arrange day by day utilization of new vegetable detailed in postponing of intellectual decline in more established age (Letenneur et al., 2007). Alzheimer's disease (AD), the most common form of senile dementia, is characterized by memory loss accompanied by worsening of basal forebrain cortical cholinergic (Korczyn & Vakhapova, 2007). The pathogenesis of AD is multifactorial and includes decline of cholinergic neurons, abnormal phosphorylation of the protein tau, oxidative stress, and altered protein processing resulting in abnormal β amyloid peptide ($A\beta$) (Korczyn & Vakhapova, 2007).

The oxidative pressure is one of most huge components for the neurodegeneration of brain prompting distinctive clutters (Halliwell, 2001). Moreover, oxidative harm is theorized as common agent for maturing and cells have a tendency to be uncovered to free radicals, which thus prompt lasting harm of brain cells and neuronal demise. Right now, Alzheimer's sickness represents enormous number of predominance, dismalness and death rate in United States and it is proposed that one in each three matured grown-ups are biting the dust with Alzheimer's illness (Devasagayam et al., 2004).

1.1. Complementary and Alternative Medicine

Complementary and alternative medicine (CAM) alludes to an extensive variety of clinical treatments outside of traditional medication (National Center for Complementary and Alternative Medicine, 2010). The expression "complementary" alludes to treatments that are utilized as a part of conjunction with regular medication, while "alternative" medicine incorporates treatments that are utilized as a part of place of traditional prescription. The expression "integrative" medication has been suggested by some CAM supplies and specialists as speaking to a combination of traditional pharmaceutical, CAM, and confirmation based prescription (Snyderman & Weil, 2002). Complementary and alternative medicine incorporates hones proclaimed to have the treatment impacts of medication however which are disproven, difficult to demonstrate, or are unnecessarily destructive in association with their impact; and where the logical conglomeration

treatment does not or can't, work in light of the fact that the known laws of nature are broken by its fundamental requires; or where it is considered such a great amount of more terrible than regular treatment that would be indecent to offer as treatment. Alternative therapies or diagnoses are not parts of prescription or science-based human services frameworks. Elective solution contains of a wide assortment of practices, items, and treatments – going from those that are biologically helpful yet not very much tried, to those with known hurtful and poisonous impacts.

Alternative medicine has a large global history (Subbarayappa, 2001) and maybe is all the more legitimately viewed as "conventional medication." As of 1997, 43% of Americans utilized some type of complementary and alternative medicine (CAM), creating 629 million have gone to and \$36 to \$47 billion consumption for every year (Eisenberg DM et al., 1998). CAM use is educated to be significantly higher among the elderly (Astin et al., 2000) (Flaherty et al., 2001). Included under this umbrella are chiropracty, dietary supplements, profound recuperating, and imagery, massage, and relaxation therapies. Examiners have discovered comparative general rates of CAM utilization, yet separate inclinations for CAM modalities among different ethnic groups (Mackenzie et al., 2003). The derisive meaning of CAM as treatments are not looking to the guidelines of the standard restorative group is progressively false. Truly, CAM has been conveyed outside of the standard human services framework, yet progressively it is offered inside healing facility settings and educated as a major aspect of conventional medicinal school syllabus (Wetzel et al., 1998).

In 1997, overview educated that 64% of US therapeutic schools offered CAM necessity as a feature of their syllabus. CAM is frequently not secured by protection (protection may cover needle therapy, chiropracty, and rub in simultaneousness with PT/OT) and 60% of patients pay completely out of pocket. CAM is normally provided by non-MD experts.

The part of restorative specialists in CAM is creating. Numerous patients don't state utilization of CAM at office visits, frequently due to their acknowledgment that therapeutic specialists will show such practices with joke. This debases the specialist understanding relationship and is a lost opportunity to talk about conceivable medication connections. The statement going before this content alludes to estrogen and is utilized to show an expanding doubt of more ordinary prescription, potentially due partially to issues, for example, these. Dynamically, it is felt that the therapeutic group has a duty to prescribe

patients at some level about CAM (Mayo Clinic Staff Complementary and alternative medicine, 2007)

1.2. Aromatherapy

Aromatherapy is the technique and exploration of utilizing plant forces, called fundamental oils, to tenderly realize change in body, brain and soul. It can help in decreasing stress, bring alleviation to solid a throbbing painfulness, help with healthy skin and skin associated issues, enhance the safe framework, lift soul and so forth. The decision of which oils are reasonable for every individual depends on numerous elements, appropriately, the word 'comprehensive', implies entirety. Fragrance based treatment is an elective field of pharmaceutical utilized for the treatment or forbiddance of diseases. It involves use of herbal oils (Kim & June, 2007), (Rho et al., 2006). It includes utilization of natural oils (Kim & June, 2007), (Rho et al., 2006). Aromatherapy is the act of utilizing unpredictable plant oils, contains critical oils, for mental and physical prosperity. Essential oils, the unadulterated substance of a plant has been dicovered to supply both mental and physical advantage when it's utilized precisely and securely. The Essential Oil Profiles zone points of interest more than 90 basic oils. Aggregates, CO₂' s and Hydrosols are likewise appropriately utilized in fragrance based treatment. Albeit basic oils, CO₂ extracts and aggregates are refined in various behavior, the term basic oil is here and there utilized as a part of composing as a sweeping term to incorporate CO₂'s and sums.

Aromatherapy initiates the limbic framework and passionate focuses of the brain, enact warm receptors, and execute microorganisms and parasites. Aromatherapy is utilized as a part of the treatment of various diseases, for example, bronchitis, exhaustion, headaches, respiratory infections, skin break out, joint inflammation, solid a throbbing painfulness, cystitis, icy and influenza. Fragrant healing likewise energizes passionate peace and tranquil with a tenderly laying impact on brain, body and feelings. Aromatherapy is a non specific term that shows to any of the diverse conventions that makes utilization of basic oils now and again in mix with other alternative medical practices and otherworldly convictions. Well known utilization of these items contains massaging products, pharmaceutical, or any topical application that coordinates the utilization of fundamental oils to their items. It has particular Western money and persuading. Therapeutic treatment including sweet-smelling blends may exist outside of

the West, however could possibly be incorporated into the term 'aromatherapy' (Rho et al., 2006; Ohio, 2008).

1.2.1. Classification of Aromatherapy

1.2.1.1. Cosmetic Aromatherapy

This treatment employs confirmed basic oils for hair restorative items, skin, body, and face. These items are utilized for their diverse impact as cleaning, saturating, drying and conditioning. A healthy skin can be picked up by utilization of essential oils in facial items. On an individual level, corrective aromatherapy of full body or foot shower will be a straightforward and a compelling method to have an affair. Similarly, few drops of reasonable oil give a restoring and renewing knowledge (Ziosi et al., 2010).

1.2.1.2. Massage aromatherapy

The utilization of grape seed, almond, or jojoba oil in unadulterated vegetable oil amid kneads has been appeared to have great influence. This is additionally recognizable as mending touch of massage therapy (Soden et al., 2004; Chang, 2008).

1.2.1.3. Medical aromatherapy

The organizer of present day aromatherapy Rene-Maurice Gattefosse has utilized essential oils to massage patients amid surgery, hence using the medicinal aromatherapy information of the impact of essential oils on empowering and treating clinically analyzed medical disease (Maeda et al., 2012).

1.2.1.4. Olfactory aromatherapy

Inhalation of essential oils has offered ascend to olfactory aromatherapy, where basic inward breath has brought about strengthened enthusiastic health, smoothness, unwinding or restoration of the human body. The arrival of stress is merged with enchanted fragrances which open notice recollections. Essential oils are supplemented to

medicinal therapy and can ever be possessed as a substitution for it (Price, 1993; Maxwell-Hudson, 1995).

1.2.1.5. Psycho-aromatherapy

In psycho-aromatherapy, distinct conditions of states of mind and feelings can be picked up by these oils giving the joy of calmness, fortification or a pleasant memory. The inward breath of the oils in this treatment is straight however the imbue in the room of a patient. Psycho-aromatherapy and aromacology both handle with the examination and impact of smell be common or engineered. Psycho-aromatherapy has limited itself with investigation of normal essential oils (Perry, 2006).

1.3. Dementia

Dementia is a disorder distinguished by disturbance of various brain capacities, including memory, considering, introduction, understandings, figuring, learning limit, dialect, and judgment. Awareness isn't blurred. The harms of insightful capacity are regularly went with, and here and there went before, by fall in passionate control, social acts, or inspiration (WHO, 2008), (WAR, 2009). Alzheimer disease is the most widely recognized type of dementia and conceivably gives to 60-70% of cases. Different sorts of dementias incorporate vascular dementia, dementia with Lewy bodies, and a group of diseases that give to frontotemporal dementia. The limits between subtypes are shady and blended structures frequently exist together (Jotheeswaran et al., 2010). Dementia can influence a man in different ways, and improvement of the malady depends upon the impact of the illness itself and the individual's identity and condition of wellbeing. Dementia can be isolated in three stages:

A- Early stage – first year or two

B-Middle stage – second to fourth or fifth years

C-Late stage – fifth year and after

These periods are given as an expected rule and not all people with dementia will demonstrate similar side effects.

1.4. Alzheimer's Disease

Alzheimer's disease (AD), the most surely understood sort of dementia, is a degenerative issue of the cerebrum that prompts memory misfortune (Alzheimer's ailment, 2010). Promotion impacts 5.3 million Americans and is the seventh driving explanation behind death in the United States. There are two driving sorts of the infection. Familial AD impacts people more young than 65, speaking to right around 500,000 AD cases in the United States alone (Alzheimer's sickness, 2010). Whatever remains of AD cases happen in adults developed 65 and more settled and is arranged as sporadic AD. The regularity of AD differentiates among an extensive variety of components, including age, co-morbidities, genetic qualities, and guideline level. There is no genuine method to clearly investigate AD without accomplishing an examination. There is no treatment for AD, however encouraging inventive work for early recognition and treatment is in advance.

1.4.1. The History and Definition of Alzheimer's Diseases

The past Greek and Roman logicians and specialists or doctors detailed the advancing of dementia identified with seniority (Berchtold & Cotman, 1998). Alois Alzheimer was found Auguste D is a primary example in lady and she had a 50 year-old and known as Alzheimer's infection in 1901 that he was a German specialist. Alois watched test till Auguste D go in 1906, from that point onward, first report distributed on it (Maurer et al., 2003). Eleven cases with similar manifestations in the following 5 years were accounted for by therapeutic analysts, by and large, they utilize term Alzheimer's ailment (Berchtold & Cotman, 1998). Emil kraepelin portrayed the AD out of the blue subsequent to checking all indications and tests revealed in unique perception of Auguste D (Berrios, 1990). He contained AD, so Kraepelin called Presenile Dementia, similar to one a player in decrepit dementia in the 8 release of his Textbook of Psychiatry, on 15 July, 1910 (Kraepelin & Diefendorf, 2007).

Until the most recent years of the twentieth century, the disclosures of Alzheimer's sickness were leaded to people in the interim the ages of 45 and 65 who expanded indications of dementia. In 1977 and after the gathering on AD the name of illness modified, they derived that the therapeutic signs of presenile and feeble dementia were for all intents and purposes comparable, nonetheless, the essayists likewise expanded this did

not law and base out the inevitability that they had unmistakable examples (Katzman et al., 1978). This in the end caused to the distinguishing proof of AD isn't reliant on age (Boller and Forbes, 1998). The word feeble dementia of the Alzheimer compose (SDAT) was used for a timeframe to clarify the status in those over 65, with the standard Alzheimer's sickness being used to recognize the individuals who were more youthful. At long last, the word Alzheimer's illness was formally acknowledged in therapeutic lexicon to clarify people of any age with a predetermined open sign model, infection period, and neuropathology (Amaducci et al., 1986).

1.4.2. Stages of Alzheimer's disease

1.4.2.1. Early-Stage Alzheimer's disease

This light stage, which more often than not endures four to two years, is frequently when the infection is first analyzed. From this period, family and companions may starts to discover that there has been a lessening in the patient's psychological limit. Normal indications at this stage incorporates (Alzheimer's Association, 2010)

- A- Difficulty holding new data.
- B- Difficulty with taking care of issue or settling on choice. Patients may start to experience difficulty sorting out funds or other instrumental exercises of day by day living.
- C- Individuality alters. The individual may start to haul out socially or display absence of incitement.
- D- Difficulty communicating contemplations.
- E- Misplacing things or getting lost. The patient may have scarcely moving in commonplace rural areas.

1.4.2.2. Moderate Alzheimer's disease

The longest phase of the disease is moderate phase enduring two to ten years. Patients regularly encounter developed trouble with memory and may require bolster with exercises of every day living. A side effect much of the time educated inside this stage incorporates (Alzheimer's Association, 2010).

- A- Progressively misguided thinking and vulnerability. The patient may start to beguile relatives, lose introduction for time and put, and may start strolling, making it perilous for them to be deserted alone.
- B- Hardness supplement compound errands, including a large number from influential exercises of every day living, for example, overseeing funds, shopping for food, arranging, and association.
- C- Greater memory misfortune. Patients may initiate to overlook subtle elements of their own history.
- D- Important identity changes. The individual may wind up noticeably pulled back from social associations and develop surprisingly high far fetched of parental Figure s.

1.4.2.3. Severe Alzheimer's disease

In this last phase of the diseases, subjective limit keeps on lessening and physical capacity is gravely influenced. This stage can last in the vicinity of 1 and 3 years. Because of the family's diminishing capacity to nurture the patient, this stage regularly brings about nursing home or other long haul mind office arrangment. Basic side effects showing in this stage incorporates (Alzheimer's Association, 2010)

- A-Loss of capacity to interface. The patient may even talk short expressions, yet can't proceed with a sensible discussion.
- B-Dependence on others for individual care, for example, eating, showering, covering and toileting numerous patients end up noticeably uncontrolled.
- C-Incapacity to work physically.

1.4.3. Risk Factors

1.4.3.1. Age

The single greatest hazard factor for building up Alzheimer's infection is age. Most instances of AD are appeared in more seasoned grown-ups, ages 65 years or above. Between the ages of 65 and 74, around 5 percent of individuals have AD. For those more than 85, the hazard grows to 50 percent (Alzheimer's Association, 2010).

1.4.3.2. Genetics

In sporadic AD, there does not seem, by all accounts, to be a hereditary example of legacy. An association Apolipoprotein E (ApoE) has been discovered between a gene and the improvement of AD. Cholesterol conveys in the blood by need protein incharged by this gene. One type of the gene, ApoE4, has been displayed to extend the opportunity of building up the illness. Nonetheless, the ApoE2 frame shields from the illness (AHAF, 2010). In the cases happening before age 65, a difference in chromosomes might be at fault. This odd type of the ailment is called Familial Alzheimer's ailment and it influences under ten percent of AD patients. It is created by changes on chromosomes one, fourteen, and twenty one. On the off chance that one chromosome change is acquired, the individual will in all probability grow AD. Posterity has a 50 percent chance (Emilien et al., 2004)

1.4.3.3. Education

There might be a combination between instructive scale and the hazard of growing AD. Individuals with less years of instruction sound to exist elevate hazard. The precise reason for this correlation is unrevealed; however it is guessed that an advanced teaching level prompts the arrangement to greater extent synaptic associations in the brain. This makes a "synaptic save" in the brain, empowering patients to reward for the loss of neurons as the illness advances (ADFAP, 2010).

1.4.3.4. Coexisting Health Problems

There is an intense correlation between cardiovascular health and brain health. The elevated pressure cause to cholestrole raised its hazards for AD growing and for diabetes it's same.

1.4.4. Pathophysiology of AD

1.4.4.1. Neuropathology

Alzheimer's disease mentioned by Abatement or loss of neurotransmitters and neurons in the cerebral cortex and other subcortical zones. This diminishing or need impact on development decay of the included territories, contain new process in the fleeting flap and parietal projection, and districts of the frontal cortex and cingulate gyrus. Debauchery additionally exists in brainstem cores like the locus coeruleus (Braak & Del, 2012). Researchers utilizing PET and MRI have revealed diminish in the volume of pointed cerebrum areas in individuals with AD as they advanced from mellow subjective harm to AD, and in grouping with same pictures of fine wellbeing more seasoned grown-ups (Moan, 2009).

Alzheimer's D harmed amyloid plaques and neurofibrillary tangles in the focal sensory system watched By utilization of magnifying lens unmistakably (Tiraboschi et al., 2004). Tangles are absolutely of the microtubule-related protein tau which have changed over hyperphosphorylated and gathered inside the cells themselves, also Plaques are thick and high fixation, to a great extent not ready to arrangement stores of beta-amyloid peptide and cell material out of neurons. Additionally various more established people develop some portion of plaques and tangles because of old years, the brains of patient with AD have a bigger measure of them in uncommon mind parts, for example, the transient projection (Bouras et al., 1994). Lewy bodies aren't rare in the focal sensory system of patients with Alzheimer's D (Kotzbauer et al., 2001).

1.4.5. Diagnosis of Alzheimer's disease

According to two segments the finding of AD. The initial handles with the reactions seen inside a patient's life and incorporates evaluating the decrease of discernment, including memory, act, talk and appreciation. Different exams are utilized by authorities to recognize the scope of the mischief, and when rehashed as regularly as adequately conceivable can supply qualities of the development of the ailment. Exams of recognition are performed, consistently begin with the clear screening test Mini-Mental State Examination (MMSE) (Folstein, 1975) , and supplemented by more experienced

neuropsychological tests e.g. WAIS or CERAD, to see harms in memory, dialect, perceptual aptitudes, thought, accommodating limits, presentation, basic reasoning and valuable limits (Figure 1.1).

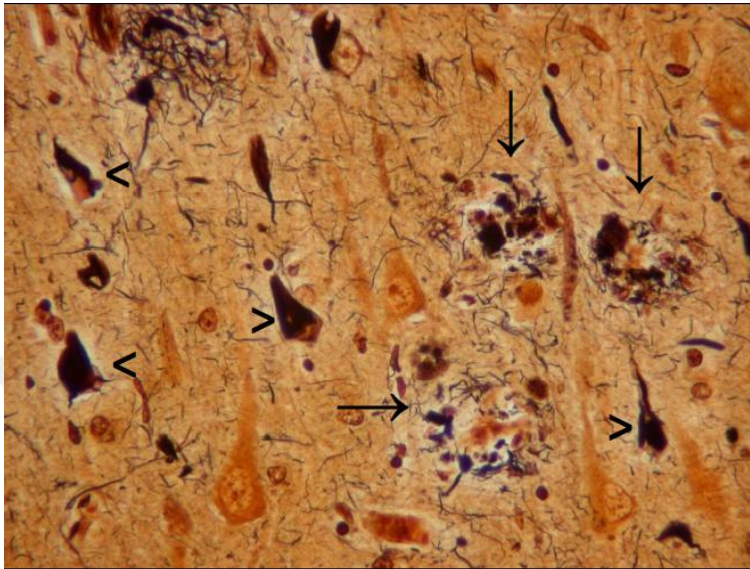


Figure 1.1. Senile plaque (SP; bolts) and neurofibrillary entanglements (NFT; pointed stones) Discolored with Bielschowsky silver staining – the two principle signs of Alzheimer's disease.

1.4.6. Symptoms of Alzheimer's disease

Albeit the progressive cognitive reduce of a patient determined Alzheimer's disease, every singular advances through the bearig of the illness remarkably. Beginning indications are regularly wrong to stage of life related issues or stress-persuaded measures, counting the incapacity to frame new recollections and review as of late learnt substances. These exact issues in the 'pre-dementia' arrange more often than not go unnoticed or might be perceived as 'mild cognitive impairment' (MCI). Beginning times from the illness view behavioral, mental changes, and additionally a progressive incapacity to bargain ordinary day by day exercises, including recently learned abilities. Typically a patient can run their own particular issues, despite the fact that their vocabulary and language familiarity shelter be observably influenced now of the illness. ultimate periode of AD need entire -reliance on a parental Figure, driving in a few cases to an aggregate loss of discourse and took after by a misfortune in bulk because of absence of portability, eventually making the patient end up noticeably bound to bed, Delusional side effects and anxiety, faltering, antagonistic

vibe and meandering shelter turn out to be less normal than in the transitional phases from illness. After death investigations of AD patients' brains (Figure 1. 2).

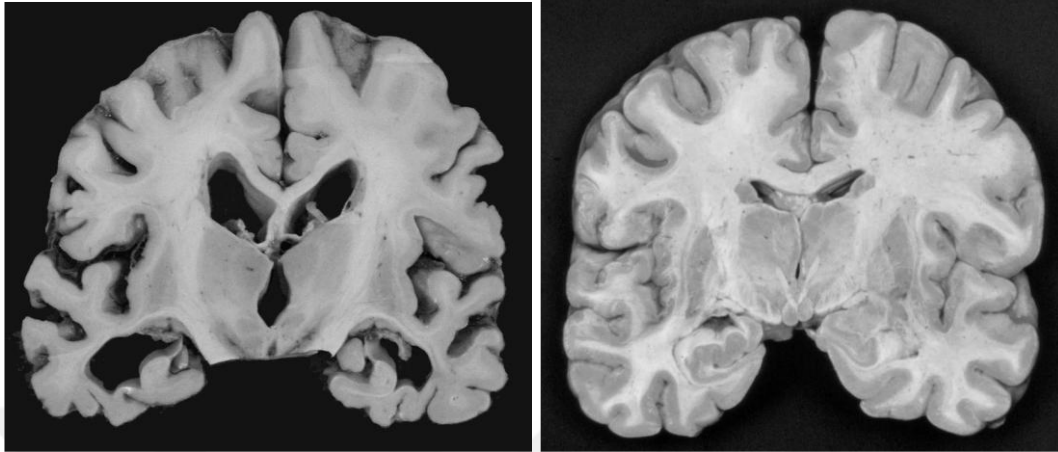


Figure 1.2. Diagram showing the decrease of an AD patient's brain (right) contrasted to a normal undemented individual's brain (left). The leading affected areas are the cortex and hippocampus.

1.4.7. Causative theories

1.4.7.1. Brief history of causes

Alois Alzheimer in 1907 clarification of the disease (Alzheimer, 1907), Alzheimer disease effected by numerous theories. The relation was found in 1960 'between the numbers of NFT and SP and psychological decrease, starting up examinations for the reason backwards these neuropathological sores (Lage, 2006). Although was not while in 1970's, that AD was formally recorded as a disease and never again thought about a piece of typical maturing, as described in the audit (Lage, 2006).Categorized as a disease, AD pulled in escalated explore into its causes. Piece of information of tremendous measures of the metal aluminum discovered in NFT in AD patients' brains (Perl & Brody 1980, Terry & Pena, 1965). AD affected by this metal according to theories that extrem. This theory is for the most part let go these days, because of for the most part fortuitous piece of information. Latest speculations encompassing AD pathogenesis include the acknowledgment of phenomenal or colossal measures of the particles discovered in SP and NFT inside AD patients'brains, for example, A β peptide. A few scientists have

recommended uneven characters in the cerebrum's homeostatic condition could cause AD (Lage, 2006).

1.4.7.2. Cholinergic hypothesis

The cholinergic theory was estimated in light of the fact that examination demonstrated that AD brains had bring down levels of acetylcholine – a main neurotransmitter in the brain – than non-unbalanced aged cases (Contestabile, 2010). Cholinergic hypothesis is one of the ancient seasoned causal hypotheses of AD, the disruptions in the cholinergic framework have additionally been the concentration of most medications accessible obtainable, despite the fact that they neglect to supply much advancement in posponding clinical side effects from illness.. Cholinergic hypothesis treated of Alzheimer's disease depended on (Donepezil, Rivastigmine and Tacrine and Soforth.)

1.4.7.3 Amyloid theory

Ultimate ordinarily upheld theory for the reason for AD connects with a protein communicated in numerous cells, of obscure capacity and incriminated in familial AD because of changes in the gene that code for it (Wisniewski, Wisniewski and Wen 1985). Despite the fact that its capacity isn't entirely comprehended, β -amyloid forerunner protein (A β PP) is recommended to be basic for neuron advancement (Vasto et al., 2008,), flagging, and may likewise work as a cell reinforcement (Crouch, 2007), and a metalloprotein, regulating copper transport and digestion (Kong et al., 2007). Source protein, the 695-770 amino acids A β PP, in most cells writes experiences the non-amyloid genic pathway. At numerous locales inside the cell including the trans-Golgi arrange, mitochondrial envelope and plasma envelope Cleavage of the A β PP protein can happen (Rogaeva et al., 2007).

1.4.7.4. Tau theory

At the moment that neuron loss and SP don't correspond weel (Gómez-Isla et al. 1997), the consideration has rotatetd across the last famous typical of AD brains, encouraging the thought known as the 'tau hypothesis'(Iqbal, 2009). The other significant

sign of AD includes a protein that encourages tubulin gathering into microtubules, which encourage the formation and adaptability of the cell (Lace, 2007). Tau utilizes supplanted joining isoforms and phosphorylation to implement its functions in the central nervous system and particularly in neurons (Lace, 2007).

1.4.8. Other potential causes

1.4.8.1. Other Hypotheses

A neurovascular theory have been proposed which depict that low utilitarian of the blood mind square might be unpredictable (Deane & Zlokovic, 2007).

The cell homeostasis of biometals like ionic iron, copper and zinc is hindered in Alzheimer's D, despite the fact that it remains undiscovered whether this is made by or makes the impacts in proteins. These particles influence and are changed by tau, APP, and APOE (Xu et al., 2014), and their dysregulation may cause oxidative pressure that may adjust to the pathology (Pohanka, 2013). Some pursuits have clarified a raised danger of developing Alzheimer's D with natural causes, for example, the inward breath and processing of metals, for instance, aluminum (Brewer, 2012). The nature of a piece of these inquires about has been reprimanded (Lidsky, 2014), and different explores have contemplated out that there is no association between disclosure to aluminum or to silica and the expansion of Alzheimer's D (Yegambaram et al., 2015).

Smoking is one of huge hazard factor for Alzheimer's D (Cataldo et al., 2010). Other hazard factors are fundamental indicatives of the innate resistant framework are for late-beginning Alzheimer's D (Eikelenboom et al., 2010).

There is contingent sign that disclosure to air contamination might be a factor to the expansion of Alzheimer's D (Moulton et al., 2012).

1.4.9. Treatment of Alzheimer's disease

There are different drugs that have been demonstrated to moderate disease movement and treatment side effects; however there is recently no treatment for AD. At the point when treatment is starting for AD patients, doctors isolate the side effects into "intellectual" and "behavioral and mental" classes (Alzheimer's Association, 2010). This

empowers treatment that is particular to the side effects being experienced. Intellectual manifestations influence memory, dialect, judgment, and thought advance. Behavioral indications change a patient's activities and feelings.

1.4.9.1. Treatment for Cognitive Symptoms

Changing the impact of concoction ambassadors in the mind required to Treatment of mental reactions. The Food and Drug Administration (FDA) has supported two sorts of remedy for this point (Alzheimer's Association, 2010). The fundamental sort is known as a cholinesterase inhibitor, which discourages the protein responsible for the fold of acetylcholine in the mind. Acetylcholine is a basic neurotransmitter required in learning and memory. Run of the mill developing causes a slight reduce in acetylcholine focus, causing infrequent obliviousness. In any case, in AD, the fixation can be reduced by as much as 90%, realizing basic memory and behavioral rot (Williams, 1998).

1.4.9.2. Treatment for Behavioral and Psychiatric Symptoms

Incorporation psychological and utilitarian decrease, AD can cause extreme behavioral and mental side effects. These side effects incorporate stress, restlessness, trouble, mind flights, and hallucinations (ADEAR, 2008). Potential treatment techniques include non-sedate intercessions and prescriptions to treat the side effects being displayed. Changing the environment to expel impediments and increment security is a compelling non-medicate approach². Plausibility is investigating any conceivable cooperation between the patient's meds that could make ominous impacts conduct or mental health. In the event that these contributions don't enhance the manifestations, medicine might be required. There are numerous drugs that could be picked depending on the indications. For instance, if the patient is encountering wretchedness, an energizer, for example, Prozac or Zoloft can be advised. Antipsychotics and anxiolytics might be taken to diminish pipedreams and anxiety, individually (Alzheimer's Association, 2010)

1.4.10. Effects of medicinal plants on Alzheimer's disease and memory Deficits

Probiotics have been informed for their efficacy to improve memory (Lyte, 2011). Probiotics are used as antidepressant in AD. It decreases worry like behavior and attenuates psychological stress.

Neurochemicals are created by microbes. Immunological and neurological influences are persuaded by probiotics. Probiotics also have immunomodulating activity (Misra & Medhi, 2013). In Chinese and Ayurvedic medicines, medicinal plants are used to treat AD, neurodegenerative changes and cognitive diseases. Different western medicines being used in memory loss are obtained from plants. Plant obtained alkaloids such as anticholinesterase have been used to treat AD. In the United Kingdom, plant obtained galantamine is also used in the treatment of neurodegenerative disorders. Five million Americans are suffering from AD and this number will expand up to 7.7 million in 2030. Symptoms of neurodegenerative confusions clearly come out after 60 years of age (Chengxuan et al., 2009). Etiology of neurodegenerative confusion is related to genetic flaw that is 10–15% of approximate cases. In AD, loss of neurons shows in subcortical structure, cortex and hippocampus. Different combinations have been recognized by phytochemical studies such as alkaloids, sterols, triterpenes, polyphenols, tannins, flavonoids and lignins that have pharmacological activities including anti-cholinesterase and anti-amyloidogenic.

Medicinal plants are playing an important role in the management of AD and memory shortage. The important traditional therapeutic methods are Ayurvedic, homeopathy, Unani and Sidha systems of medicine. Unani system of medicine offers traditionally a hugely scientific health care therapy as a divine gift and as a result the global interest of the medical occupation is concentrated on medicinal plants. Traditional system of medicine is basically inhibitory, protective, nutritive and remedial. Therefore, traditional medicines are safe and harmless which treat the patients with fewer or no side influences.

Herbal medicines have their origins in ancient cultures, including those of the Egyptian, Indians and Chinese. It requires the use of medicinal plants to treat AD and improves general health and well initiates. In fact, many pharmaceutical drugs are based on the synthesized adaptations of naturally happening combinations discovered in plants. In recent years, interest in herbal medicine has expanded, leading to a greater scientific

interest in the medicinal use of plants in treating illness and improving health, often without any important side influences. Herbal medicines and natural products are the oldest cures known to humanbeing. Medicinal plants have been used by all cultures throughout the history. In exist scenario; the requirement for herbal products is developing, exponentially throughout the World. In human body, the nervous system harmonizes and controles the different voluntary and involuntary activities of the body. The central nervous system and the autonomic nervous system are interlinked and some drugs affect the CNS producing reactions connected with the autonomic system (Mc Corry, 2007). Drugs participated with the CNS may have general stimulatory or sedative action with anticonvulsant and psychopharmacological activities. Memory shortage is a major global health problem.

Current therapies are insufficient and have huge unfavourable influences. There is an urgent need for potential alternative treatments for AD and memory deficiency. Different medicinal plants are adviced to improve the memory. We have reviewed the literature on medicinal plants used in the treatment of AD and memory deficiency (Xu et al., 2009).

Several medicinal plants have been used for decades in different cultures to enhance memory such as *Valeriana officinalis*, *Punica granatum* L., *Salvia officinalis*, *Myristica fragrans* *Bacopa monnieri* L., *Centella asiatica* Linn and *Evolvulus alsinoides* L. (Elufioye et al., 2012).

Other plants having memory enhancing properties are *Juglans regia* (Haider et al., 2011), *Cuminum cyminum* (Koppula and Choi, 2011), *Ficus religiosa* (Kaur et al., 2010), *Melissa officinalis* (Kennedy and Scholey, 2006), *Rosmarinus officinalis* (Ozarowski et al., 2013), *Piper nigrum* (Hritcu et al., 2014), *Ginkgo biloba* (Tan et al., 2015), *Bacopa monnieri* (Roodenrys et al., 2002), *Desmodium gangeticum* (Mahajan et al., 2015) and *Emblica officinalis* Gaerth (Justin Thenmozhi et al., 2016).

1.5. *Juniperus oxycedrus* subsp. *oxycedrus*

Juniperus L. (Cupressaceae) is a genus incorporates more than sixty species and is totally across the board in the northern side of the equator (Adams 2008). In Turkey the *Juniperus* genus by eleven taxa performed in Turkey, the most well-known being *Juniperus oxycedrus* subsp. *oxycedrus* (Tumen et al., 2010) (Figure 1.3).



Figure 1.3. *Juniperus oxycedrus* subsp. *oxycedrus* twigs and berries from Turkey

Morphologically, *J. oxycedrus* is a champion among the most specific taxa in the fragment *Juniperus*. As showed by DNA progression examinations among *Juniperus* species inside the red seed cone gather around the Mediterranean territory, the difference of *J. oxycedrus* inside a sub-clade *oxycedrus*-*cedrus* is clearly specific from *deltooides-brevifolia*-*navicularis* (Adams and Schwarzbach, 2012).

The foamed cone focus of *J. oxycedrus* is for the most part used as a piece of Turkey in the treatment of gastrointestinal agitating impact, typical colds, as an expectorant, to treat calcinosis in joints, as a diuretic to treat kidney stones, against urinary aggravations, hemorrhoids, and as a hypoglycaemic (Sezik et al. 2001).

Juniperus wood berries and leaves have been used since old conditions, and were known as a cure-all cure in the medieval times; they were used by and large as aroma, as a diuretic and against destructiveness (Tumen et al. 2010).

The basic oil of *J. oxycedrus* from various plant organs has an extensive variety of employments in sustenance, makeup and pharmaceutical ventures also. Moreover, numerous investigations concerning its natural action (cell reinforcement, antimicrobial, antifungal, and so forth.) have additionally been accounted for (Derwich and Chabir, 2011).

J. oxycedrus used in battling distinctive diseases prompt their mitigating, cancer prevention agent, antimicrobial and cicatrizing properties. Their oils contained high measures of mono and sesqui-terpenes.

The members of *juniperus* genus has widely distributed all over the world. Two juniper species occur in western Arabia: *Juniperus phoenicea* L. and *Juniperus procera* Hochst. ex Endl. A third juniper, *Juniperus excelsa* M. -Bieb. subsp. *polycarpus* (K.Koch) Takhtajan, is restricted in Arabia to the northern mountains of Oman. This subspecies is distributed in the mountains of Turkey, Kirgizistan, Baluchistan in Pakistan and India (Farjon, 1992)

The Aims of The Study

The *Juniperus oxycedrus* subsp. *oxycedrus* is a medicinal plant naturally grown in Turkey and the other parts of the World And also used for this purpose in Turkey. The main goal of this study is to assess the potential neuroprotective activities of *Juniperus oxycedrus* Subsp. *oxycedrus* essential oil and possible components in scopolamine- treated rats. To reach this purpose a number of ther studies will also be carried out. These include the exam of chemical configuration of the *Juniperus oxycedrus* essential oil. Other specific aims include the possible effects of *Juniperus oxycedrus* on spatial memory in Y-maze task, and in radial arm-maze task, as well as antidepressant activity in forced swimming test and anxiolytic activity in elevated plus maze. The potential influence of the essential oil on oxidative stress status in scopolamine –persuaded rats will also be assessed.

We selected the *Juniperus oxycedrus* subsp. *oxycedrus* plant because of it was possible for cultivation as an ornamental shrub in southern Europe..where in some numbers of cultivars. especially with much more pendulous foliage. were commonly have been planted in gardens and parks. Essential oils were extracted from the branches and leaves by destructive distillation, especially in France and Turkey..This 'oil of cade' was used for medicinal target. such as to prepare empyreumatic oil.. It has been antiseptic and antiparasitic properties. and antidepression. Rectified cade oil was also used look likes a fragrance component in soaps, detergents,creams, lotions and perfumes (McMinn & Maino., 1981).

2. MATERIALS AND METHODS

2.1. Plant Materials and Volatile Oil Preparation

Aerial parts of *juniperus oxycedrus* were collected in Palu district (Elazig), Eastern Anatolian region of Turkey. The samples of the plants were identified and voucher specimen have been registered and Stored in the Herbarium of Firat University (FUH), for ready reference. The twigs (100 g) were used to obtain the oil and it was removed by hydro-distillation for 3 h using a Clevenger-type equipment.

2.2. Extraction Oil Procedure

Twigs of the plant, dried in shade, and then smashed into small parts and hydrodistilled by using Clevenger-type equipment (Fig. 2.1). Also, this is the most low-priced, usual and simplest process of removal. This type of remove shows to the best process for leaves, nuts, roots, stems, and other part of the plant or for powders. The basic profits and rediginous of these manners are that more oil process, the lower water vapor is used and lesser time for the process. The parts of plant are warmed by haze that between plant parts or by adding it in boiling water. The result of haze and healing is a cause to collapse and explode the cell structure of the herb parts, Eventually the essential oils removed. The haze of boiled water carried essential oil molecules through pipe and channel with a cooling pool after returning to the liquid shape and gathered in where they return to the liquid form and are collected in a bent part of the equipment. The appearing liquid is a complicated of water and oil, since not water melt essential oils, unconnected and usually lighter collected on the surface of water in the tub, the next step is unconnectedly envoy water and oil off (Zainal et al., 2015) for 3 hours the oil was removed (Figure 2.1).`



Figure 2.1. Clevenger-type apparatus

2.3. Chromatographic Analyses of Essential Oil

2.3.1. GC- FID Analyses

GC-FID (Agilent 6890 GC) is an instrumental way to examine of Essential oils. We used GC- FID for the examining of the essential oils and screening of the chemical conformation in the oil. This tool contains a column of HP-5 MS (30 m $\times$ 0.25 mm i.d., film thickness, 0.25 μ m) and sensor or tracer in Plant Products and Biotechnology Research Laboratory (BUBAL) in Firat University (Figure 2.2).

2.3.2. GC-MS ANALYSES

To identify various materials in samples that used for tests usually Gas chromatography–Mass spectrometry (GC-MS) is used. Also GC-MS uses contained environmental analysis, identification of unknown samples, drug detection, explosives

examination; fire examination and consisting that part of samples have taken of herb (Figure 2.2).



Figure 2.2. GC-MS (Agilent 5973 N) and GC-FID (Agilent 6890 GC) system

2.4. Animal Modelling

In the firstly we utilized fourty tow male rats nearly weighting 250 to 50 g. divided into 6 groups each group contain seven rats: (1) Control group (2) Scopolamine (Sco) - alone-treated (3) Diazepam alone-treated (4) Tramadol alone treated (5) Scopolamine-treated gathering got *J.oxycedrus* subsp. *oycedrus* fundamental oil 1% (Sco+ JEO 1%) and (6) Scopolamine-treated assembling got *J.oxycedrus* subsp. *oycedrus* essential oil 3% (Sco+JEO3%). Control, DZP, TRM-and scopolamine alone-treated gatherings were put in confines in the comparative circumstances however without of the accomplished basic oil. They were treat with to take in 0.9% saline with 1% Tween 80 game plan.

2.5. Inhalation apparatus and drug administration

The Inhalation contraption contains a Plexiglas chamber (50 x 40 x 28 cm) (Figure 2.3). one chambers used for the attempted creatures were Two chambers utilized, and other one used to control and scopolamine alone-treated creatures. 1% Tween 80 (v/v) utilized to

weakened *J. oxycedrus* fundamental oil . *J.oxycedrus* fundamental oil presentation (200 μ l, either 1% or 3%) was by methods for an electronic vaporizer (Oregon Scientific WS113) put at the base of chamber, yet unreachabeable of the creatures. (Gradinariu et al., 2014).Chambers constantly washed (10% ethanol game plan) after completed each gathering rats presented to oil vapors by *J.oxycedrus* fundamental oil for controlled 15 min period, step by step, for 21 days.



Figure 2.3. Inhalation apparatus

2.6. Y-maze test

Short-term memory evaluated by spontaneous alternation behavior in the Y-maze task. The Y-maze was utilized as a part of the present investigation contains of three arms (35 cm long, 25 cm high and 10 cm wide)(Figure 2.4.) and an equilateral triangular focal territory. 15 min after the inward breath of *J. oxycedrus* fundamental oil (JEO1% and JEO3%), rats were set at at the center of the three arms of Y- maze task and permitted to move freely through the Y- maze task for 8 min. An arm entry was computed when the hind paws of the rat were totaly within the arm. Spontaneous alternation behavior was defined as entries into all three arms on successively selected. The amount of higher number of spontaneous alternation behaviors was then the total number of arms entered minus 2 per spontaneous alternation X 100 (Hritcu et al., 2014).

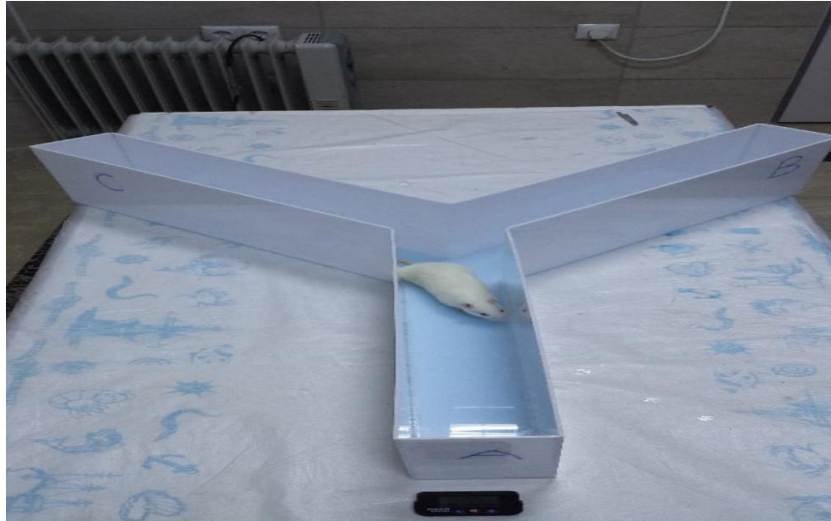


Figure 2.4. Y-maze task apparatus

2.7. Radial arm-maze test

The radial arm-maze contained of 8 arms utilized as a part of the present examination, numbered from 1 to 8 (48 cm x 12 cm), (Figure 2.5.) extending radially from a focal zone (32 cm in breadth). The device was set 50 cm over the floor, and encompassed by various additional maze visual signs set at a similar place amid the investigation. , three or four rats were in a similar time set in the The radial arm-maze allowed to find for 5 min and take the sustenance openly Prior to the genuine preparing initialed. The food was at first set all through the maze, yet was advance bye step restricted to the sustenance container . In the instructional meetings, just 5 arms were goaded (nos. 1, 2, 4, 5, and 7) .



Figure 2.5. Radial arm-maze test apparatus

2.8. Elevated plus-maze test (EPM)

The EPM contains of four arms, 49 cm long and 10 cm wide, and raised 50 cm above the ground. Two arms were enclosed by walls 30 cm high and the other two arms kept open. Each rat was placed in the center of the maze apparatus facing to one of the closed arms. for 5 min, and the time spent and number of entries into the open and enclosed arms was computed (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) are calculated (Figure 2.6).



Figure 2.6. Elevated plus-maze test apparatus

2.9. Forced swimming test (FST)

The FST is the most broadly utilized model for assessing depressive-like reaction (Cryan et al., 2002). The depressive-like reaction was assessed, essentially utilizing a similar route clarified by Campos, Fernandes in 2005, however with alteration. On the main day of the investigations (pretest session), rats were separately moved into round and hollow beneficiaries (breadth 30 cm, stature 59 cm) comprising 25 cm of water at $26 \pm 1^\circ\text{C}$. The creatures were abandoned to swim for 15 min before being diverted, dried and come back to their pens. The methodology was rehashed 24 h later, in a 6 min swim session (test session), 15 min after the inward breath of *S. multicaulis* fundamental oil (JEO1% and JEO3%). Amid the test session, the accompanying behavioral reactions were enrolled: (1) fixed status (time went through gliding with the insignificant developments to keep the head over the water); and (2) swimming (time went through with dynamic swimming developments) (Figure 2.7).



Figure 2.7. Forced swimming test apparatus

2.10. Statistical analysis

Behavioral scores inside Y-maze, radial arm-maze, changed pluse-maze and forced swimming tests were analyzed by one-way analysis of variance (ANOVA) followed by Tukey post hoc test utilizing GraphPad Prism 6 programming for Windows. In order to evaluate differences between groups in the radial arm-maze task unconnected repeated measures ANOVA were calculated on the number of working memory errors and the number of reference memory errors with groups (Control, Sco, Sco+ JEO1% and JEO3%), as between-subject factor and days (1 to 7) as with in subjects factors. All results are communicated as mean $\pm$ standard error of mean (S.E.M). F values for which $p < 0.05$ were viewed as statistically significant.

3. RESULTS

3.1. Chemical Compounds of the *Juniperus oxycedrus* subsp. *oxycedrus* Essential Oil

The main chemical combination of the *J. oxycedrus* ssp. *oxycedrus* essential oil was examined by GC–FID/MS (Table 3.1). The whole amount of 48 different combinations was unconnected which constituted 89.3% (w/w) of the total extracted essential oil. The important and fundamental compounds of the essential oil were monoterpene hydrocarbons (C₁₀H₁₆), contain α -pinene (42.9 %), β -pinene (3.8 %), β -myrcene (3.9 %) and limonene (17.8 %) that calculated for 68.4 % of the complete extracted essential oil (Figure 3.1).

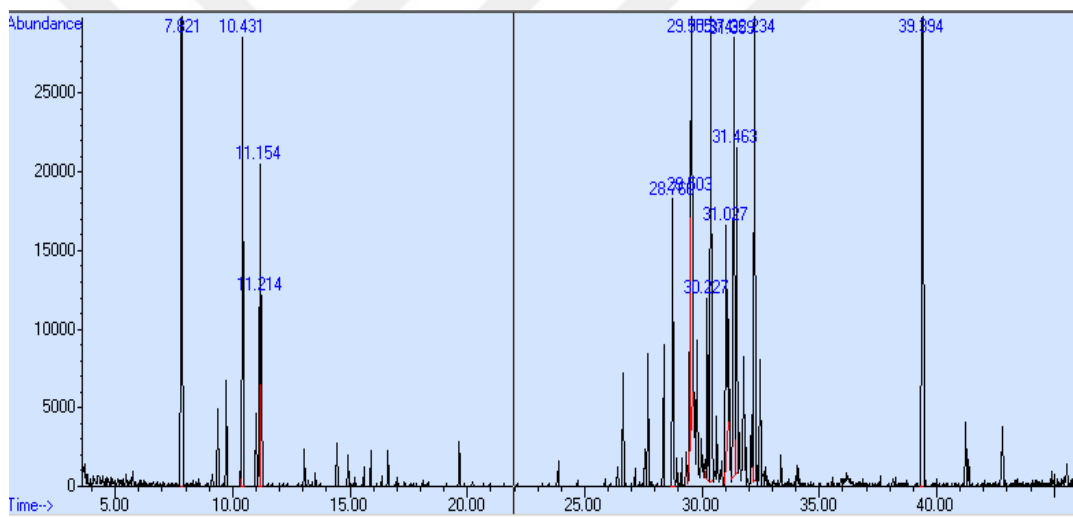


Figure 3.1. Chromatograph of *Juniperus oxycedrus* essential oil

Table 3.1. Chemical Compounds of the *Juniperus oxycedrus* subsp. *oxycedrus* Essential Oil

No	Constituents	RI (Retention Index)	Concentration
1	α-pinene	1021	42.9
2	Camphene	1034	0.8
3	β-pinene	1055	3.8
4	β-myrcene	1063	3.9
5	α -Terpinene	1071	0.2
6	Δ 3 carene	1078	0.1
7	Benzene, 1-methyl-2	1091	0.1
8	Limonene	1094	17.8
9	β -phellandrene	1096	0.8
10	1,3,6 Octatriene	1107	0.1
11	γ -terpinene	1116	0.1
12	α -terpinolene	1136	0.6
13	Benzene 1 methyl 4	1140	0.1
14	3 cyclopentene-1 acetaldehyde	1167	0.1
15	Borneol L	1199	0.1
16	3- cyclohexen-1-ol, 4 methyl -1	1205	0.1
17	α -terpineol	1214	0.3
18	Endobornylacetate	1281	0.3
19	Benzene, 1methoxy-4	1283	0.3
20	2,4 Decadienal 1312 0.6	1312	0.6
21	α -cubebene	1336	0.1
22	α -copaene	1359	0.1
23	β -caryophyllene	1392	1.6
24	α -humulene	1418	1.3
25	1-dodecanol	1429	0.4
26	3-buten-2 one	1432	0.1
27	Germacrene D	1434	1.1
28	Methyl-isoeugenol 1442 0.2	1442	0.2
29	α -muurolene	1446	0.3
30	γ -cadinene	1455	0.2
31	Δ -cadinene	1458	0.2
32	3-hexen 1ol, benzoate	1490	0.1
33	Caryophyllene oxide	1498	5.1
34	Humulene epoxide II	1514	2.4
35	α -cadinol	1538	0.6
36	Pentadecanal	1569	0.1
37	Benzyl benzoate	1596	0.1
38	n-hexadecanoic acid	1690	0.1
39	Abietatrene	1756	0.2
40	1-phenanthrene carboxaldehyde	1838	0.4
41	Abietal	1861	0.3
Total			88.9

3.2. Effect of *Juniperus oxycedrus* subsp. *oxycedrus* Essential Oil on Memory in Y-maze Task

In order to examine spatial working memory, Y-maze task was used. One way-ANOVA showed differences overall between all groups [$F(3, 12) = 6.858, p < 0.01$] in the spontaneous alternation % in Y-maze task.

The Tukey's post hoc test showed significant differences between control group vs. Scopolamine group ($p < 0.05$), Scopolamine group vs. Sco. + jeo1% group ($p < 0.05$), and Scopolamine group vs. Sco. + jeo3% group ($p < 0.01$) for the spontaneous alternation percentage (Figure 3.2).

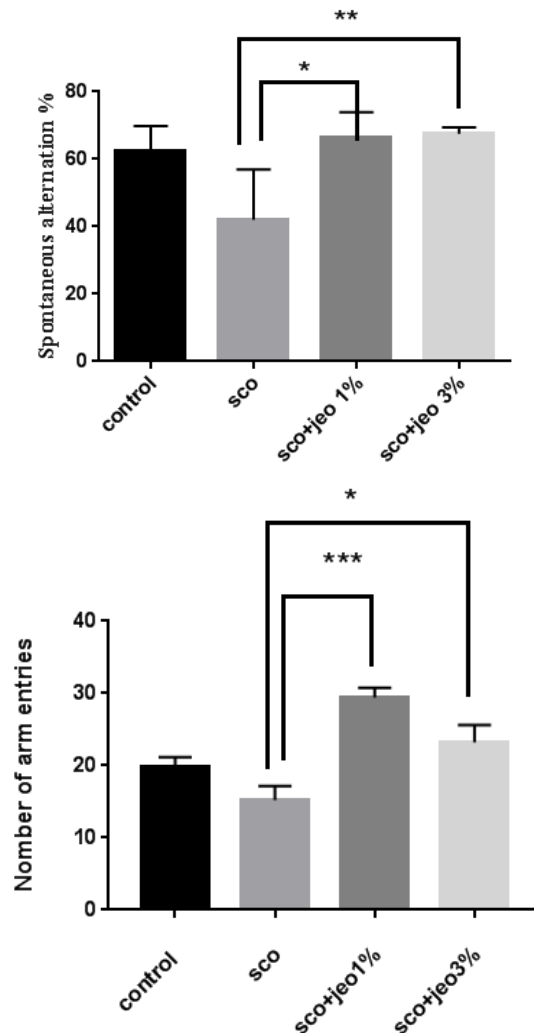


Figure 3.2. Effect of *Juniperus oxycedrus* essential oil (jeo1% and jeo3%) in the Y-maze task on a) spontaneous alternation %, b) number of arm entries in the scopolamine (Sco.)-treated rats.

3.3. Effect of *Juniperus oxycedrus* subsp. *oxycedrus* Essential Oil on Memory in Radial Arm-maze Task

To evaluate the effects of inhaled *J. oxycedrus essential* oil on the spatial memory formation, radial arm-maze task was also used. Repeated-measures ANOVA detected a significant group difference ($F(3,16) = 5.476, p < 0.01$) for working memory errors (Figure 3.3 a.). Furthermore, repeated measures ANOVA detected a significant time difference ($F(6, 96) = 4.494, p < 0.001$) and a significant group difference ($F(6, 96) = 4.441, p < 0.05$) for reference memory errors (Figure 3.3 b.).

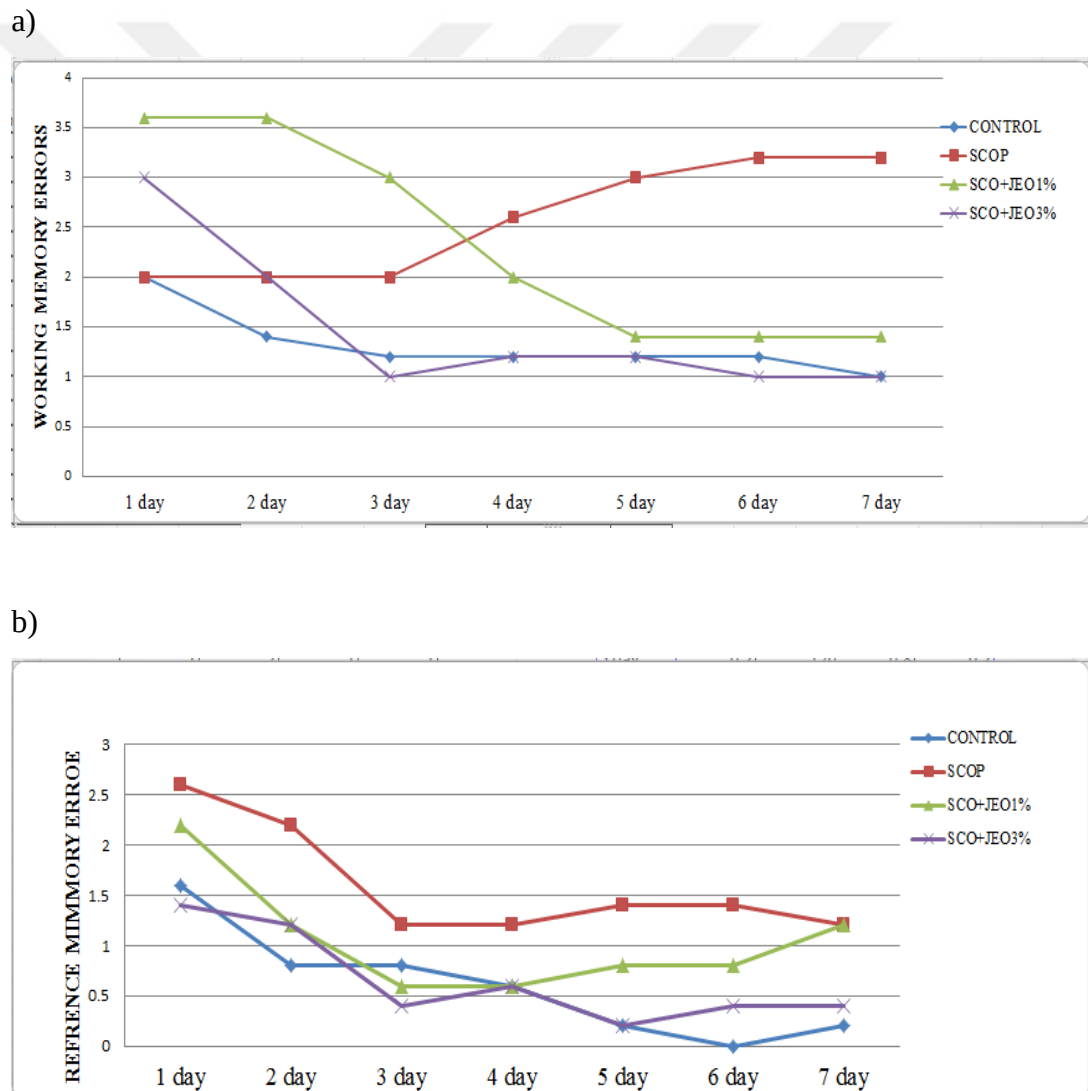


Figure 3.3. Effects of inhaled *Juniperus oxycedrus* essential oil (jeo1% and jeo 3%) during 7 days training on the a) working memory errors and b) the reference memory errors in the radial arm-maze test.

3.4. Effects of *Juniperus oxycedrus* Essential Oil on Anxiety in Elevated Plus maze Task

For the number of open-arm entries the EPM task ANOVA detected a significance total influence ($F(4,20) = 16.73$, $P < 0.0005$), and, Tukey's post hoc examination explored a significant difference between control vs. DIAZ group ($P < 0.0005$), DIAZ group vs. scopolamine ($p < 0.0001$), DIAZ group vs. Sco+jeo 1% ($p < 0.005$), DIAZ group vs. Sco+jeo 3% ($p < 0.0005$), and Scopolamine group vs. Sco. + jeo1% group ($P < 0.05$) for the number of open-arm entries (Figure 3.4 a.). for the number of crossings, ANOVA also detected a significance total influence ($F(4,20) = 53.11$, $P < 0.0001$), as well as for the percentage of open arm time ($F(3,12) = 7.2222$, $p < 0.005$). Tukey's post hoc test explored significant differences between control vs. DIAZ group ($P < 0.0001$), control group vs. Scopolamine group ($p < 0.0005$), control group vs. sco+jeo 3% ($p < 0.001$), DIAZ group vs. Scopolamine ($p < 0.0001$), DIAZ group vs. Sco+jeo 1% ($p < 0.0001$), DIAZ group vs. Sco+jeo 3% ($p < 0.05$), Scopolamine group vs. Sco. + jeo1% group ($P < 0.0001$), Scopolamine group vs. Sco.+ jeo3% group ($P < 0.0001$), and scopolamine group vs. sco+jeo3% ($p < 0.05$), for the number of crossings (Figure 3.4 b.). Also for the percentage of open arm time (Figure 3.4.c), Tukey's post hoc examination explored significant differences between control vs. sco+jeo3% ($p < 0.05$), scopolamine group vs. sco+jeo1% ($p < 0.05$), and scopolamine group vs. sco+jeo3% ($p < 0.01$)

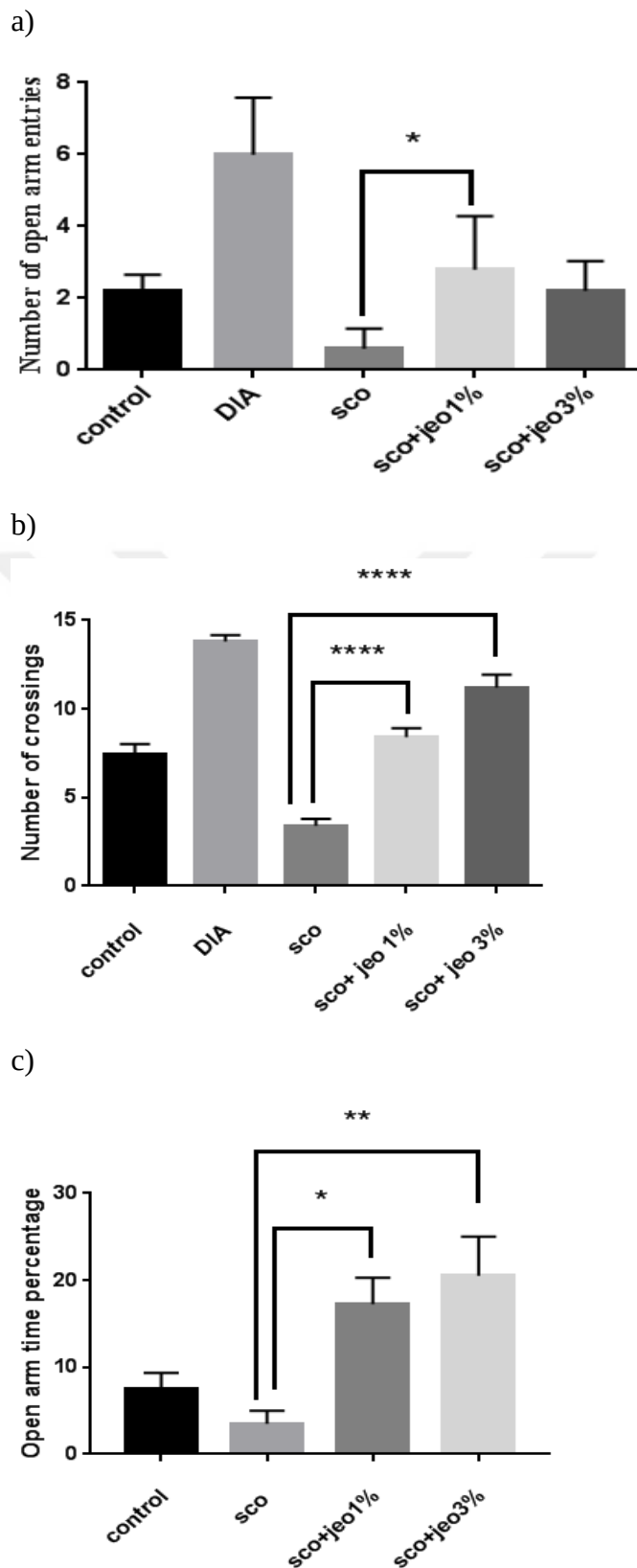


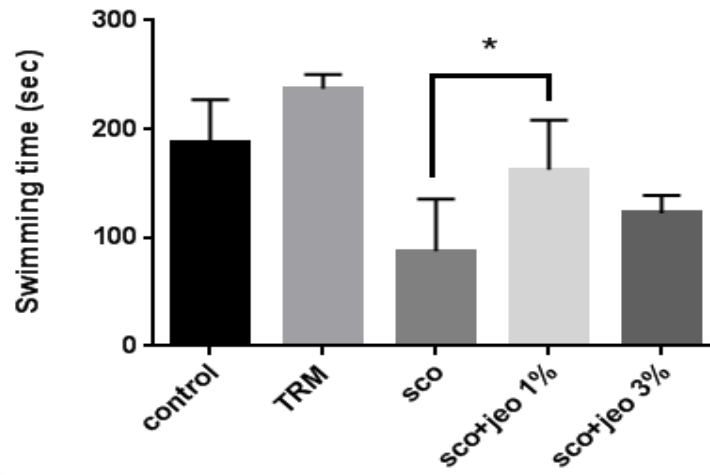
Figure 3.4. Effects of the inhaled *Juniperus oxycedrus* essential oil (jeo1% and jeo3%) in the elevated plus-maze test, in the scopolamine (Sco.)-treated rats on a) number of open-arm entries, b) number of crossings c) percentage of open arm time

3.5. Effects of *Juniperus oxycedrus* subsp. *oxycedrus* Essential Oil on Depression in Forced Swimming Task

In the FST, ANOVA detected a significance total influence on the immobility time ($F(4, 20) = 38.71$, $P < 0.0001$), and on the swimming time ($F(4, 25) = 15.61$, $P < 0.0001$). Also Tukey's post hoc test detected significant differences for the swimming time (Figure 3.5 a.), between TRM group vs. Scopolamine group ($P < 0.0001$), control group vs. scopolamine group ($P < 0.001$), control group vs. sco+jeo3% ($P < 0.05$), TRM group vs. Sco. +jeo1% group ($P < 0.05$), TRM group vs. Sco. +jeo3% group ($P < 0.0001$), Scopolamine group vs. Sco. + jeo1% group ($P < 0.05$),

Additionally, Tukey's post hoc examination detected significant differences between control group vs. TRM group ($P < 0.001$), control group vs. scopolamine group ($P < 0.0001$), control group vs. Sco. + jeo3% group ($P < 0.05$), TRM group vs. the Scopolamine group ($P < 0.0001$), TRM group vs. Sco. +jeo1% group ($P < 0.0001$), TRM group vs. Sco +jeo3% group ($P < 0.0001$), Scopolamine group vs. Sco. + jeo1% group ($P < 0.005$) and Scopolamine group vs. Sco. +jeo3% group ($P < 0.05$) for the immobility time (Figure 3.5 b.).

a)



b)

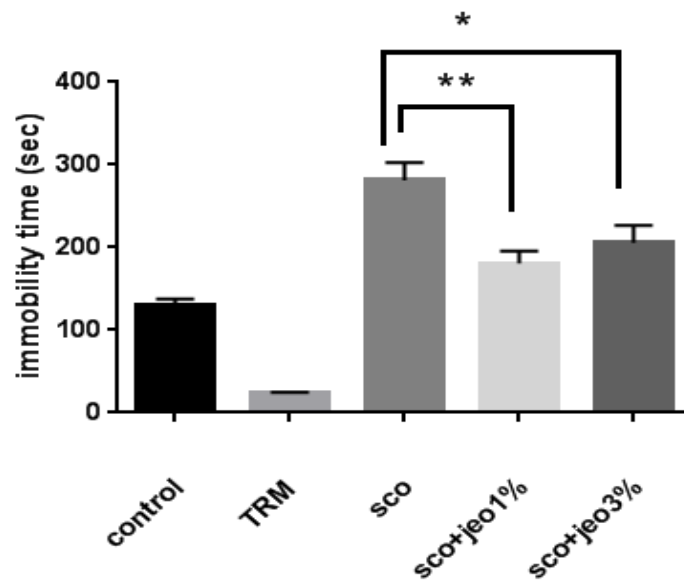


Figure 3.5. Effects of the inhaled *Juniperus oxycedrus* essential oil (jeo1% and jeo3%) in the forced swimming test, in the scopolamine (Sco.)-treated rats, on a) swimming time and b) immobility time.

4. DISCUSSION AND CONCLUSION

4.1. Discussion

One of the ancient therapies is the use of aromatic herbs for alleviation of numerous illnesses. In actual fact, aromatic herbs have been used for thousands of years by different people in all countries in the world, like Turkey and Iraq. Pharmacological searches provide scientific assists in the traditional and conventional utilize of aromatic, medical herbs and aromatherapy; however, most clinical investigations are required regarding to their power to be effective in arranging to set up a direction for their use in ordinary health care (Linck et al., 2009).

Table 2 has been shown the major compounds of the *Juniperus* genus members. The table has shown the essential oil composition of the juniperus species has shown similarity in view of some compounds reported by some researchers (Table 4.1).

Table 4.1. Major Compounds of Essential Oil of Different *Juniperus* Species

	Major Compounds	<i>J.oxycedrus</i> (This study)	<i>J. phoenicea</i> (Derwich et al.,2010)	<i>J. berry</i> (MartinaHöferl et al .,2014)	<i>J. rigida</i> (Qiaoxia o Liu, 2016).	<i>J. Monsperma</i> (Robert et al., 2014)	<i>J. excelsa</i> (Ehsani et al., 2012).
1	α -pinene	42.9	32.49	51.4	20.8	51.3	79.9
2	Camphene	0.8	-	-	-	-	-
3	β -pinene	3.8	52.79	5.0	27.0	1.1	0.8
4	β -myrcene	3.9	-	-	-		-
5	α -Terpinene	0.2	-	0.1	-	0.1	-
6	Δ 3 carene	0.1	-	-		-	-
7	Benzene, 1-methyl-2	0.1	-	-	-	-	-
8	Limonene	17.8	-	5.1	5.76	2.6	1.36
9	β -phellandrene	0.8	-	0.5	-	7.5	-
	Total	65.6	85.2	61.6	53.56	62.6	82.06

According to our thesis with *J. phoenicea* the level of α -pinene and Limonene lower than our thesis (32.49), and the level of β -pinene more than ours (52.79) (Derwich et al., 2010) and according to our result with *J. berry* the level of α -pinene and β -pinene (5.0) both of them higher than our results and the level of Limonene lower than ours (Martina Höferl et al., 2014). According to our result with *J. rigida* the level of α -pinene (20.8) and Limonene (5.76) lower than our results and the level of β -pinene (27) more than ours (Qiaoxiao Liu, 2016).

According to our result with *J. monspersma* the level of α -pinene (51.3) and higher than our results and the level of β -pinene (1.1) and limonene (2.6) lower than ours (Robert et al., 2014). When compared the results of this study with the *J. excels*; the level of α -pinene approximately (79.9) higher than our results and the level of β -pinene (0.8) and limonene (1.36) lower than our reports (Ehsani et al., 2012).

The extracted essential oil of *J. oxycedrus* which examined by the GC-FID/MS are monoterpene hydrocarbons and contain α -pinene (42.9 %), β -pinene (3.8 %), myrcene (3.9%), and limonene (17.8 %) that calculated for 68.4 % of the total *J. oxycedrus* extracted, as the significant constituents of the removed oil that these combinations could be inclined for the watched anxiolytic antidepressant-like act in scopolamine-treated animals. From α -pinene (42.9%) was identified in huge numbers and it has been published to exhibit anxiolytic results (Kasuya et al., 2013; Satou et al., 2014). The monoterpene limonene (17.8 %) recognized in *J. oxycedrus* essential oil as the chief and important active chemical part exhibited antidepressant-like and calmative-like action and result was published (Guzmán-Gutiérrez et al., 2012).

The both doses (especially the lower dose) of *J. oxycedrus* essential oil in scopolamine-treated rats significantly improved spatial working memory in the Y-maze task, as proved by the development of spontaneous alternation percentage as compared to scopolamine alone-treated rats. Our conclusion suggests that the both doses of *J. oxycedrus* essential oil (1 and 3 %) used in our research improved the short-term memory in the Y-maze task in scopolamine-treated rats. Though, no significant differences were observed between 1% and 3% dose of *J. oxycedrus* essential oil on spatial working memory in the Y-maze task.

Our research was additionally planned to look at anxiety and depressive-like reaction after the inward breath of the *Juniperus oxycedrus* essential oil (1% and 3 %, in 14

consecutive days) in rats objection or case to take of scopolamine via injection. Accordingly, go up against scopolamine reason an anxiety like conduct and depressive-like reaction in agreement with our early and front verifications (Hughes et al., 2004) (Smythe et al., 1996). In a research that calculated light-dim predominance, it was spreaded that scopolamine (2 mg/kg) persuaded the measure of going to the light side (Hughes et al., 2004). Also, in the black-white apparatus, scopolamine (2 mg/kg) was gained to grow picked up to develop uneasiness related conduct on the two activities related, also activity non-related parameters (Smythe et al., 1996).

The elevated plus-maze is diagnosed as a precious model to predict the anxiolytic or anxiogenic-like effects of drugs (Aydin et al., 2015). The percentage of the amount of crossings and the number of open-arm entries significantly decreased by injection of scopolamine in the elevated plus maze task, two demonstrator parameters of uneasiness. This data that showed. This demonstrates the scopolamine-treated rats experienced extremely measures of nervousness and were appropriate for estimating the potential anxiolytic issues as *J. oxycedrus* essential oil (Hayashi et al., 2012).

Moreover, at that point the scopolamine-treated rats being breathed in *J. oxycedrus* basic oil (JEO1% and JEO3%), the % of number of arm crossings significantly elevated in the Sco.+ JEO3% group as versus with scopolamine-alone treated rats. What's more, amount of open arm entries elevated in the Sco +JEO 3% as versus with scopolamine-alone treated rats. Critical differences seen in the vicinity of 1% and 3% of *J. oxycedrus* removed essential oil (JEO1% and JEO3%) on the % of number of arm crossings, on the number arm time percentage and on the number of open arm entries in the elevated plus-maze test.

These influences are the facts that the benzodiazepine diazepam (DZP), celebrate as positive standard anxiolytic (Mansouri et al., 2014), was used as a positive control connected to the *J. oxycedrus* essential oil (JEO1% and JEO3%) in total, this experimental situation. As expected, DZP made significant increase in the percentage of number of arm crossings and the number of open-arm entries and also increase in the number arm time percentage as compared with scopolamine-alone treated rats. These numbers are stable with the conclusions of high amounts of anterior researches, which have clues that DZP and other benzodiazepines make significant anxiolytic impressions in a diversity of anxiolytic screening methods, containing elevated plus-maze test methods (Marco Leggio et al., 2014; Adebessin et al., 2015).

The pharmacological action of diazepam upgrades the influence of the neurotransmitter GABA by attaching to the benzodiazepine site on the GABAA receptor guidance to central nervous system (CNS) depression (Riss et al., 2008). The anxiety markers in the elevated plusmaze (the % of number of arm crossings and the amount of open-arm entries) explored up being sensitive to the stewards, which were reflection to process via the GABAA receptor complex (Emamghoreishi et al., 2005). Furthermore, it has been documented that β -pinene exhibited antidepressant-like and calmativ-like or downer act and work (Guzmán-Gutiérrez et al., 2012).

A preceding research displayed no contrast between the potentiated reaction or restraint of GABA on GABAA receptors in the presence of α -pinene and β -pinene (Aoshima and Hamamoto, 1999), nformed that both have a calmativ influence. In light of these reports, this high- α -pinene (31.25 %) and β -pinene (4.58 %) containing *J.oxycedrus* essential oil has built up the anxiolytic-like conduct and against depressive-like reaction in scopolamine-treated rats.

The immobility time significantly increased were infusion by scopolamine and swimming time significantly decreased as versus with the control group rats, two indications parameters of discouragement, in our results that displays (Bonito-Oliva et al., 2014). This markED the scopolamine alone treated rats displayed depression. At that point being displayed to 1% and 3% of *J.oxycedrus* essential oil (JEO1% and JEO3%), the immobility time significantly reduction particularly in the Sco. + JEO1% also the swimming time significantly elevated, especially in the Sco. + JEO1% was additionally watched. These conclusions recommended that *J.oxycedrus* removed essential oil, however especially JEO1%, groups an effective upper like response to an irremediable pressure.

The immobility time significantly decreased were injected by tramadol (TRM) and swimming time significantly increased as versus with scopolamine-alone treated rats in the recent research. Tramadol is an only medicine treat with more styles of act. It is a weak agonist of the μ - opioid receptor, but it also prohibits the reuptake of serotonin as well as norepinephrine. It is an analgesic, and it is also to assume as an antidepressant (Caspani et al., 2014).

Furthermore, it is significant to be attend that oxidative stress permitts as true, to be a serious factor in Alzheimer's D (Budzynska et al., 2014). The CNS is more ready and sensitive to oxidative stress as the brain has a much use of oxygen, having high numbers of free-radical generating iron and matters like ascorbate, glutamate and polyunsaturated fatty

acids, that is normal to pass redox-reaction and guidance to radicals' forming and displays comparatively weak antioxidant defends systems (Walton et al., 2012). Scopolamine is confederated with elevated oxidative stress in the ctotal brain, also in especially organizations relied with remembering and teach (Pachauri et al., 2012).

4.2. Conclusion

Taking together, our findings recommend that *Juniperus oxycedrus* subsp. *oxycedrus* (Cupressaceae) essential oil to make a better spatial memory formation and reduced anxiety and depressive like behavior according to the statistical tests used. In addition, it also displayed the antioxidant influences by reduction of oxidative stress. Also, in some exams 1% and in some other 3% of essential oil had more activity, but we recommended to use that 1% of *J. oxycedrus* essential oil, because this percentage had more positive result on the animal modelling rat for both behavioral and chemical tests. But the study has need more developed research, by biocemically and more.

We were revaluation item about the management of AD and the medicinal plants with possible therapeutic values in our paper. The herbal therapy is helps to discount the symptoms related to AD and now expect to control AD improvement. Herbal therapy can improve the life quality of patients with AD and memory deficits. Worldwide research is being done to find effective treatment of AD. This paper determines that herbal therapy is an encouraging choice as alternative to treat AD. Medicinal plants used in different systems of medicine particularly Unani system of medicines exhibit their powerful role in the management and cure of memory disorders.

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