THE NEUROPROTECTIVE EFFECTS OF INHALED *Hypericum scabrum* L. (HYPERICACEAE) ESSENTIAL OIL AGAINST SCOPOLAMINE-INDUCED ALZHEIMER'S TYPE DEMENTIA

Tariq Hassan MOHAMMED SUR
(142110112)

Master Thesis
Department: Biology
Supervisor: Prof. Dr. Eyüp BAĞCI
FEBRUARY-2017

REPOPLIC OF TURKEY

FIRAT UNIVERSITY

DEPARTMENT OF BIOLOGY

THE NEUROPROTECTIVE EFFECTS OF INHALED *Hypericum scabrum* L. (HYPERICACEAE) ESSENTIAL OIL AGAINST SCOPOLAMINE-INDUCED ALZHEIMER'S TYPE DEMENTIA

Master Thesis
Tariq Hassan MOHAMMED SUR
(142110112)

Supervisor
Prof. Dr. Eyüp BAĞCI

FEBRUARY-2017

ELAZIG

REPUBLIC OF TURKEY

FIRAT UNIVERSITY

GRATUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

THE NEUROPROTECTIVE EFFECTS OF INHALED *HYPERICUM SCABRUM* L. (HYPERICACEAE) ESSENTIAL OIL AGAINST SCOPOLAMINE-INDUCED ALZHEIMER'S TYPE DEMENTIA

Master's Thesis

TARIQ HASSAN MOHAMMED SUR

(142110112)

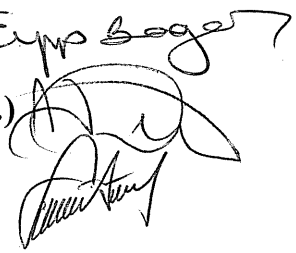
Date of the Thesis submission to: 18.01.2017

Date of Defense: 03.02.2017

Thesis Supervisor: Prof. Dr. Eyüp BAĞCI (F.Ü.)

Other Jury Members: Prof. Dr. Hasan Çetin ÖZEN (D.Ü.)

Doç. Dr. Abdullah ASLAN (F.Ü.)



FEBRUARY-2017

ACKNOWLEDGEMENT

I express sincere appreciation to Prof. Dr. Eyup BAGCI for their supervisoring, guidance and insight throughout the research, and to Res. Asst. Emel AYDIN for helping in all research duration.

I express my thanks and appreciation to my family especially my parents, my wife and my very cute son Mohammed for their understanding, motivation and patience.

Lastly, I am thankful to all colleagues and friends who made my stay at the Firat University a memorable and valuable experience.

LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

The Neuroprotective Effects of Inhaled *Hypericum scabrum* L. (Hypericaceae) Essential Oil Against Scopolamine-Induced Alzheimer's Type Dementia

ABSTRACT

Alzheimer's disease is a neurodegenerative illness with no effective treats for now. In this study *H. scabrum* has been used in traditional medicine for several years, especially in Anatolia. *H. scabrum* essential oil was analyzed by GC-MS. *Hypericum scabrum* essential oil 1% and *Hypericum scabrum* essential oil 3% groups inhaled the oil for 21 continuous days. In the essential oil the α-pinene (51.3 %) was found to be the major component. Inhalation of this oil caused to increase spontaneous alternations % in Y-maze, decreased working memory errors and reference memory errors in radial arm-maze, increased the number of open-arm entries and number of arm crossings in elevated plus-maze, also increased swimming time and decreased immobility time in forced swimming test. Elevation of GPX (glutathione peroxidase), GSH (glutathione) and SOD (superoxide dismutase), and reduction of MDA (malondialdehyde) levels in the homogenates of hippocampus and amygdala tissues of rat brains were reported in the essential oil treated rats compared to scopolamine alone-treated rats. Our study showed that, inhalation of *H. scabrum* essential oil prevents scopolamine-induced memory impairment, and reduces anxiety and depression by attenuation of the oxidative stress in the rat hippocampus and amygdala.

Keywords: Alzheimer's disease, *Hypericum scabrum*, Anxiety and Depression, Oxidative stress.

Scopolamine ile olusturulan Alzheimer tipi demansa karşı *Hypericum scabrum* L. (Hypericaceae) uçucu yağı solunumunun sinir-koruyucu etkileri

ÖZET

Alzheimer hastalığı şuana kadar bir tedavisi bulunmayan nörodejeneratif bir hastalıktır bu kalşmada. *Hypericum scabrum* özellikle Anadolu'da yıllardan beri geleneksel tıpta kullanılmaktadır. *Hypericum scabrum* uçucu yağı GC-MS ile analiz edilmiştir. *Hypericum scabrum* essential oil % 1and *Hypericum scabrum* essential oil %3 grupları 21 gün boyunca uçucu yağına maruz kalmışlardır. Uçucu yağda alfa-pinen (%51.3) 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 ve geçiş sayılarında artışa, zorunlu yüzme testinde yüzme süresinde artışa, hareketsizlik süresinde ise düşüşe yol açmıştır. Yalnız skopolamin uygulanan gruba göre ratların hipokampüs ve amigdala beyin dokularında GPX (glutathione peroxidase), GSH (glutathione) ve SOD (superoxide dismutase) seviyelerinde artış, MDA (malondialdehyde) seviyesinde ise düşüş görülmüştür. Çalışmamız *H. scabrum* uçucu yağının amigdala ve hipokampüsteki oksidatif stresi azaltarak skopolaminle oluşan hafıza geriliğini önlediğini ve anksiyete ve depresyonu azalttığını göstermiştir.

Anahtar kelimeler: Alzheimer hastalığı, *Hypericum scabrum*, Anksiyete and Depresyon, Oksidatif stres

1. INTRODUCTION

Use of herbs and herbal extracts for affording medicinal intention called Phytotherapy (Moulay et al., 2010). Also, phytotherapy is separate from anthroposophic and homeopathy medication, and abstains blending herb and artificial bioactive materials. Some regarded that phytotherapy is a part of alternative medicine. Atropine, alkaloids and morphine are some of the highest number of herbal constituents that have biological and medicinal effects, for instance, have been established through medical researches. Though about phytotherapy place and efficacy of medicinal treatments, there are numerous of debates.

The usual term that used to define progression loss of function or structure of neurons and counting the death of neurons is neurodegeneration. Numerous of neurodegenerative illnesses include Huntington's, amyotrophic lateral sclerosis, Alzheimer's and Parkinson's happen like a product of neurodegenerative progressions. These types of diseases are irremediable, resulting in death of neuron cells and / or improvement deterioration. As study developments, most likenesses to become visible that tell these illnesses to one other on a sub-cellular level. Detecting these likenesses presents hope for medicinal progress that could to remedy several illnesses concurrently. There are several equals among different neurodegenerative sicknesses counting unusual protein associations and accumulation also resulted cell death (Bredesen et al., 2006). In numerous of different steps of neuronal circuitry ranging from molecular to systemic can be found neurodegeneration.

Misfolded proteins are one of the links between neurodegenerative agitations, and founded on patient with AD. Several neurodegenerative illnesses are ordered as proteopathies as they relate to the accumulation of protein misfolded, prion: chief and original part of transmissible spongiform encephalopathies and prion illnesses, alpha-synuclein: can accumulate to shape insolvable fibers in pathological situations categorized by Lewy bodies, like numerous system atrophy, Parkinson's illness and dementia with Lewy bodies. Alpha-synuclein is the elementary structural constituent of Lewy body fibers. Also, an alpha-synuclein segment, recognized as the non-Abeta component (NAC), is located in amyloid plaques in AD, tau: hyper phosphorylated tau protein is the chief parts of neurofibrillary tangles in AD, β-amyloid: the main and more parts of senile plaques in AD.

One of common neurodegenerative illness is Alzheimer's disease or just AD, pathological multiplication of β-amyloid peptides, synaptic decrease, neurofibrillary tangles, oxidative stress, and neuroinflammation are general characterize of AD, finally guiding to decrease knowable and information (Xu et al., 2014).

Acetylcholine (ACh) hydrolyzed to acetate and choline by an enzyme that called acetylcholinesterase (AChE) or acetylhydrolase and in the resultant amount of ACh decreased in the brain. In conformity with cholinergic hypothesis, prevention of AChE activity leading to grows cholinergic functions in people with AD. The inhibitory activity of enzyme Cholinesterase, is a foundation in the treatment of AD and is a heartwarming strategy for the cure of dementia (Mathew and Subramanian, 2014).

A muscarinic recipient competitor, scopolamine, is supplied established on cholinergic hypothesis (Ebert and Kirch, 1998). Scopolamine has been employed as a mention remedy for inducement age and dementia depended cognitive shortages in intact humans and animals (Klinkenberg and Blokland, 2010). It is a well-grooved amnesic drug (Eastonn et al., 2012), damaging acquisition and remembering in rats and men, particularly in the effects of acquisition and short-term memory (Kwon et al., 2013).

The role of oxidative stress in the ethiopathogenesis of Alzheimer's D, it is known and important. There is collecting document proposing that oxidative stress is a primal incident in the growing of the illness and such oxidative modifiers are comprehensive entirely the body (Moreira et al., 2008). Importance function in creating signaling pathways guiding to cell death is suggested oxidative stress (Luque-Contreras et al., 2014). Some searches have spread the existence of high DNA, RNA, protein and lipid oxidation in central nerve system of cases with Alzheimer's D and mild cognitive impairment (MCI) (Dumont and Beal, 2011).

1.1. Alternative Medicine and Aromatherapy

Fringe medicine or alternative medicine is practiced pretended to have the recovering effects of remedy and drug but are not firmed, impossible to firm, or just injurious. Distinctions or alternative therapies are not pieces of remedy and drug or based health care methods. Fringe medicine contain of a high amount of different trainings, results, and medical treatments-rusting from those that are vitally usable and acceptable, but not experienced very

well, to those with recognized injurious and poisonous effects. Placebo may be cause to perceive the effects of fringe medicine, reduced effects of efficiently remedy, and return to the past, intend where healthy progress that would have happened anyway is related to alternative remedies. Fringe medicine is not the similar as tentative medicine.

Fringe medicine has elevated in folks and is used by a high number of the people in a high number of countries. When it widely remarked itself: from to supplementary or complementary or tricksters medicine, it boosts originally the similar trainings. Recently expositors frequently offer fringe medicine be utilized to efficiently medical remedy, in a confidence that it "complements" the remedy. Though, expressive and important medicine with reciprocal effects caused by alternative medicines may in its place negatively affect cures, creating them fewer operative, especially cancer cure. Although it is illicit to the bazaar to sell alternative remedies for most kind of cancer medicine in more of the advanced world, numerous people with cancer patients utilize them.

Treatment and diagnoses in alternative medical are not involved in the knowledge that based on an educational program study in medical centers for learning, and are not utilized in medical exercise where cures are established with scientific information. Fringe medicine is frequently established on errors in reasoning, fraud, propaganda, religion, pseudoscience, tradition, belief in supernatural energies, or superstition. Alternative medicine licensing and regulation and health care earners differ within and between countries.

Progressing fringe medicine, has been named unethical and hazardous. Analysis this type of medicine that have no technological sources has been termed a prodigality of rare medicinal study origins. Experts have believed "there is actually no such object as fringe remedy, the only medication that activities and medication that doesn't", and the difficult and object is not lone that it does not job, however that the "fundamental rationale is magical, downright illogical or puerile". Also, there have been calls that the intelligibility of any alternative medicine that acts is contradictory, as some cure confirmed to act is simply "medicine". General alternative medicine is a set of practices, products, and recommendations that are observed or believed through their consumers to give the remedial effects of drug, but the effects of these remedial has not been completely established consuming systematically (Kent, 1997; Goldrosen and Straus, 2004), or alternative medicine system and training is not

portion of medicine, or whose systems or performs are directly refuted by scientific principles or scientific suggestion utilize in medicine (Hines and Terence, 2003). "Medicine" or "biomedicine" is that portion of medical science that uses origins of physiology, biology, biophysics, molecular biology, and other ordinary sciences to medical exercise, using scientific approaches to find the effectiveness of that exercise. Different remedy, an alternative creation or exercise does not initiate from using scientific procedure, but may instead be created on fraud, testimonials, propaganda, religion, errors in reasoning, tradition, superstition, pseudoscience, belief in supernatural energies, or other unscientific bases (Hines and Terence, 2003).

In General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine, reported in 2000 by the World Health Organization (WHO), alternative medicine and supplementary were showed as a wide set of health care performs that are not fragment of that nation's own tradition and are not combined into the main health care organization (Xiaorui, 2013).

Uses of herb parts and aromatic herb oils is aromatherapy that contains essential oils, and other aroma composites for improving physical or psychological happiness and healthy.

It can be presented like a Supplementary remedy or, most controversially, like a system of alternative remedy. Supplementary treatment can be presented beside normal, usual cure (Kuriyama et al., 2005), with alternative medicine presented in its place of conformity, document-based cures. Aromatherapists, who specify in the exercise of aromatherapy, use mixtures of remedial essential oils that can be exited through kneading, thematic requisition, breathing or water afloat to instigate a wished reply and reaction.There is no good medical indication that aromatherapy can each treatment any illness or inhibits of disease, but it has ability aid to amend common and public happiness and safety (Ades, 2009).

Aromatherapy as a modes contain several applications like aerial diffusion: for environmental fragrancing or aerial disinfection, direct inhalation: for respiratory disinfection, decongestant, expectoration as well as psychological effects and topical applications: for general massage, baths, compresses, therapeutic skin care.

1.2. Dementia

Dementia (disambiguation), also noted as senility (Dementia. MedlinePlus, 2015), is a wide class of central nerve system illness that lead to a long term and frequently step-by-step reduce in the ability to opine and recall that is large enough to impact a person's day-to-day operation. Other popular symptoms contain excited problems, troubles with language, and a decrease in motive (Burns and Iliffe, 2009). A person's cognizance is usually not touched. A dementia identification needs to modify from a patient common cerebral operation and a larger, worse than one would anticipate lead to ageing (Solomon et al., 2011). These symptoms also have an important influence on a patient, caregiver.

Alzheimer's disease is the most public type of dementia. About 60% to 70% of dementia cases are AD. Vascular dementia about 25%, Lewy body dementia about 15%, and frontotemporal dementia are other common types of dementia (Burns and Iliffe, 2009). Less public causes are Parkinson's disease, normal pressure hydrocephalus, syphilis, and Creutzfeldt-Jakob disease (Gauthier and Serge, 2006). More than one kind of dementia may subsist in the same person.

Hypothyroidism Lyme disease vitamin, vitamin B12 deficiency and neurosyphillis are four basic origins of easily reversible dementia, and checking is necessary for people with remembering trouble in hypothyroidism and B12 deficiency. For Lyme illness and neurosyphilis, checking is necessary if there are risk factors for those illnesses in the individual (Solomon et al., 2011).

1.3. Alzheimer’s Disease

In AD the number of nerve cells slowly reduced. The most public first sign is trouble in memory new incidents (Burns and Iliffe, 2009). In progressive AD, difficulties with speaking, confusion, feeling swings, decrease of activity, not bring off self-care, and behavioral objects are other symptoms (Burns and Iliffe, 2009). As an individual’s status decline, they often retire from family and other people (Burns and Iliffe, 2009). Functions of body gradually decrease and finally resulting in death. However the accelerate of progress can high, the mean life suggestion after diagnoses are three to nine years (Querfurth and Laferla, 2010; Todd et al., 2013).

The causes of AD are not understood very well (Burns and Iliffe, 2009). Believed the genetic with high amount of genes make around 70% of risk for AD that is usually complicated and abstruse (Ballard et al., 2011). Other risk factors contain a record of head hurts, hypertension or depression (Burns and Iliffe, 2009). The AD effect is a companion with plaques and tangles in the central nerve system (Ballard et al., 2011). An eventual identification is depending on the disease history and cognitive and blood testing with medical imagination to rule out other feasible reasons. First indications are frequently wrong for normal ageing (Burns and Iliffe, 2009). Testing of brain tissue is necessary for a definite diagnosing (Ballard et al., 2011). Cerebral and physical activity, and keep away from obesity may to detract the risk of Alzheimer's D (Ballard et al., 2011). There are no medicaments or supplements that reduce risk.

No any drugs or other types of treatments block or reduce its progression. Touched humans with this disease increasingly rely on others for help and caregiver, in more time placing a load on the health care provider; the pressures and force can contain psychological, physical, social and economic elements (Thompson et al., 2007). Good and daily Sport training plans are favorable with regard to activity of daily living and can possible to make better outcomes (Forbes et al., 2013). Medical drug and care of behavioral troubles or psychosis refer or lead to dementia with antipsychotics is public but not ordinarily suggested due to their frequently being few useful and a raised risk of soon death.

People with Alzheimer's D in the world measured about 48 million in 2015. This disease usually started in a patient over 65 years old, but in about 4% to 5% of the samples AD started before 65, which started before this (Mendez, 2012). About 6% of humans with 65 years or older are affected (Burns and Iliffe, 2009). In 2010, dementia causes for about 486,000 deaths (Lozano et al., 2012). In industrial countries, Alzheimer's D is one of the more financially expensive illnesses (Bonin-Guillaume et al., 2005; Meek et al., 1998). In the elder people some problems seem normal. These could be: loss memory on occasion, forget the places in sometimes, short-term memory loss, not remembering perfect items. These troubles do not intend that they have AD.

1.3.1. History of AD

The past Greek and Roman philosophers and doctors or physicians reported the progressing of dementia related to old age (Berchtold and Cotman, 1998). The first sample was discovered in woman called Auguste D and she had a 50 year-old by Alois Alzheimer and known as Alzheimer's disease in 1901 that he was a German psychiatrist. Alois observed sample till Auguste D passed in 1906, after that, first report published on it (Maurer et al., 2003). Eleven cases with the same symptoms in the next 5 years were reported by medical researchers, in most cases, they use term Alzheimer's disease (Berchtold and Cotman, 1998). Emil kraepelin described the AD for the first time after checking all symptoms and tests reported in original observation of Auguste D (Berrios, 1990). He contained AD, so Kraepelin called Presenile Dementia, like one part of senile dementia in the 8 edition of his Textbook of Psychiatry, on 15 July, 1910 (Kraepelin and Diefendorf, 2007).

Until the last years of the 20^{th} century, the discoveries of Alzheimer's disease was leaded to humans in the interval the ages of 45 and 65 who increased signs of dementia. In 1977 and after the conference on AD the name of disease altered, they deduced that the medical indications of presenile and senile dementia were virtually similar, however, the writers also increased that this did not law and base out the eventuality that they had distinct samples (Katzman et al., 1978). This eventually caused to the identification of AD is not dependent on age (Boller and Forbes, 1998). The word senile dementia of the Alzheimer type (SDAT) was utilized for a period of time to explain the status in those above 65, with the standard Alzheimer's disease being utilized to identify those who were younger. Finally, the word Alzheimer's disease was officially accepted in medical dictionary to explain persons of all ages with a specified public sign model, disease period, and neuropathology (Amaducci et al., 1986).

1.3.2. Signs and Symptoms

The AD course contains 4 steps, with a growth form of cognitive and work and activity damage.

a. Pre-dementia Stage

Rapidly mistakes are early signs of disease, usually with stress or ageing (Waldemar et al., 2007). All tests of neuropsychological with details can divulge mild cognitive hard, partly 8 years before a patient fulfills carry out the pathological tests for identification of AD (Bäckman et al., 2004). These early signs can affect the more complicate daily living activity (Nygård, 2003). The more detectable shortage is short term memory decrease, which report as hardly in recalling new studied facts and it can't receive new data and facts (Bäckman et al., 2004; Arnáiz and Almkvist, 2003).

Subtle troubles with the administrative purpose of attentiveness, designing, flexibility, and dropped thinking, or damage in semantic memory can also be symptomatic of the first steps of AD (Bäckman et al., 2004). Unfeeling can be happened at this phase, and remains the most continual neuropsychiatric sign in out of the course of the AD (Landes et al., 2001). Depressive signs, excitability and decreased awareness of subtle memory hardly are also public (Murray et al., 2012). The MCI is another name for the first stage of the AD (Arnáiz and Almkvist, 2003). This transitional step usually happened between natural ageing and dementia. MCI can exhibit with a difference of signs, and when remembering damaged is the predominant sign, it is named "amnesic MCI" and is very often seen as a prodromic phase of Alzheimer's disease (Grundman et al., 2004).

b. Early Stage

In humans with AD, the acceleration impairment of understanding and memory has finally resulted in a final distinction. In a little percentage, problems with speech, executive activities, feeling or receipt, or execution of the motions is more prominent than remembering the difficulties (Förstl and Kurz, 1999). In AD all region memory not damaged equally. Older memories of the episodic memory, semantic memory, and implicit memory are caused to decrease amount of new facts or memories (Carlesimo and Oscar-Berman, 1992; Jelicic et al., 1995).

Language and speaking difficulties are generally characterized by a decrease words and terminology and reduced word fluency, finally to a full impoverishment of oral and written language (Förstl and Kurz, 1999; Taler and Phillips, 2008). In this step, the patient

with AD is ordinarily able of connecting basic ideas suitable (Förstl and Kurz, 1999; Taler and Phillips, 2008; Frank, 1994). When making fine motor tasks such as writing, drawing or clothing, many action harmony and planning problems may be exist, but they are generally not showed (Förstl and Kurz, 1999). As the illness develops, patients with AD can usually to do many tasks none dependently, but may need helps or leader with the high amount of cognitively exacting activities (Förstl and Kurz, 1999).

c. Moderate Stage

Progressive declension finally futurity independence, with persons being incapable to exits more public works of living in the day (Förstl and Kurz, 1999). Speech problems become visible due to a disability to repeat vocabulary, which results to repeated mistake word replacement. Reading and writing ability are also improvement decrease (Förstl and Kurz, 1999) (Frank, 1994). Complicated motor sequences to get decrease attuned as time running and AD growth, so the risk of falling raises (Förstl and Kurz, 1999). In this step, remembering problems worsen, and the patient may mistake to distinguish similar things (Förstl and Kurz, 1999). Long-term memory, which was before healthy and safe, to get damaged (Förstl and Kurz, 1999).

Behavioral and neuropsychiatric altered become high frequent. Public manifestations are mobile, excitability and unstable results, causing to crying, rebellions of unknowing violation, or remaining to caregiving (Förstl and Kurz, 1999). Sundowning can also come out (Volicer et al., 2001). About 30% of folk with this disease increase illusionary misidentifications and other imaginary signs (Förstl and Kurz, 1999). Patients also decrease intelligence of their illness steps and limitations. Urinary incontinence can increase (Förstl and Kurz, 1999). These signs make stress for communications and cares, which can be decrease by mobile the patient from house care to other long-term care facilities (Förstl and Kurz, 1999; Gold et al., 1995).

d. Advanced Stage

During the last steps, the patient is wholly dependent on caregivers (Förstl and Kurz, 1999). Speech is decrease to easy warding or just one word, finally resulting to wholly absence of speaking (Förstl and Kurz, 1999; Frank, 1994). Despite the loss of communicative

language ability, people in more cases able to understand and come back to moving signals. However aggressiveness can yet exist, maximum apathy and fatigue are highly public signs. Patient with AD will finally unable to do even the easy tasks freely; muscle mass and motility, decrease to the point where they are confined to bed and disable to nourishment themselves. The causes of death are generally out factors, like pneumonia, pressure ulcers or infection, not the AD itself (Förstl and Kurz, 1999).

1.3.3. Causes of Alzheimer's D

The more causes of AD cases are unknown, but genes changed made 1% to 5% of cases that have been identified (Reitz et al., 2014).

Other explained causes of disease are several hypotheses:

a. Cholinergic Hypothesis

The cholinergic hypothesis is, the oldest of which more currently present drug treatment are based (Francis et al., 1999), which suggest that the decrease synthesis of the neurotransmitter ACh are the causes of AD. The cholinergic hypothesis has not present distributed help, in high amount because medications conscious to treat acetylcholine deficiency have not been more operative (Martorana et al., 2010). Other cholinergic operate have also been suggested, for likeness, starting of large-scale accumulation of amyloid (Shen, 2004), caused to generalized neuroinflammation (Wenk, 2003).

b. Amyloid Hypothesis

In 1991, the amyloid hypothesis demanded that extracellular amyloid beta (Aβ) sediment is the important cause of the AD (Hardy and Allsop, 1991; Mudher and Lovestone, 2002). Assist for this contend comes from the position of the gene for the amyloid precursor protein (APP) on chromosome 21, in concert with the act that people with trisomy 21 who have an extra gene copy most times commonly show at least the first signs of AD by 40 years old (Nistor et al,. 2007; Lott and head, 2005). So, a special isoform of apolipoprotein, APOE4, (is a gene) is a bigger genetic risk factor for Alzheimer’s disease. Also apolipoproteins improve the destroy or separation of beta amyloid, part of isoforms are not more effective at this task (like APOE4), cause to extra amyloid produced in the central nervous system (Polvikoski et al., 1995). Advance information comes from the discovering that transgenic rat

that show a mutant form of the men APP gene grow fibrillary amyloid plaques and Alzheimer's-like brain pathology with specific acquisition shorts (Lalonde et al., 2002).

An empiric vaccine was discovered to clean the amyloid plaques in first patient tests, but experimental vaccine didn't have each significant results on dementia (Holmes et al., 2008). Investigator has been guided to surmise non-plaque Aβ oligomers (totality of high number monomers) as the first pathogenic shape of Aβ. These toxic oligomers, also concerned to as amyloid-derived distributed ligands (ADDLs), bond to a surface receptor on neurons and modify the form of the synapse, thereby break up neuronal relationship (Lacor et al., 2007). One receptor for Aβ oligomers may be the prion protein, the same protein that has been joined to mad cow disease and the connected human status, Creutzfeldt–Jakob disease, therefore possible attaching the underlying system of these neurodegenerative confusions with that of AD (Lauren et al., 2009). One research found possible grounds of human to human transmitting (Jaunmuktane et al., 2015).

c. Tau Hypothesis

The tau hypothesis suggest that tau protein abnormality begins the illness cascade (Mudher and Lovestone, 2002). In this model, hyperphosphorylated tau starts to even with other threads of tau. Finally, they make neurofibrillary tangles inner bodies of nerve cell (Goedert et al., 1991). When this happens, the microtubules modify, extinguish the structure of the cell's cytoskeleton, which prostrations the neuron's transport system (Iqbal et al., 2005). This may causes prior in failure in biochemical relation between neurons and second in the destroy of the cells (Chun and Johnson, 2007).

d. Other Hypotheses

A neurovascular hypothesis have been suggested which describe that low functional of the blood brain block may be complex (Deane and Zlokovic, 2007).

The cellular homeostasis of biometals like ionic iron, copper and zinc is interrupted in Alzheimer's D, although it stays undiagnosed whether this is made by or creates the effects in proteins. These ions affect and are changed by tau, APP, and APOE (Xu et al., 2014), and their dysregulation may cause oxidative stress that may modify to the pathology (Su et al., 2008; Kastenholz et al., 2009; Pohanka, 2013). Some searches have explained an elevated risk

of growing Alzheimer's D with environmental causes such as the inhalation and digesting of metals, for example, aluminum (Brewer, 2012). The quality of a part of these researches has been criticized (Santibáñez et al., 2007; Lidsky, 2014), and other researches have reasoned out that there is no connection between revelation to aluminum or to silica and the increase of Alzheimer's D (Yegambaram et al., 2015).

One of significant risk factor for Alzheimer's D is smoking (Cataldo et al., 2010). Other risk factors are systemic indicatives of the inborn immune system are for late-onset Alzheimer's D (Eikelenboom et al., 2010).

There is conditional indication that revelation to air pollution may be a factor to the increase of Alzheimer's D (Moulton et al., 2012).

1.3.4. Risk Factors

a. Age

The largest discovered risk factor for AD is increasing age. Alzheimer's is not a portion of natural biological process, but your risk factor development after your age attain to 65 years old. The range of dementia increased two time every 10 years after age 60 years old. Folk with uncommon genetic exchanges linked to early-onset AD start to show signs as early as their 30s.

b. Genetic and Family History

Risk of AD increased in you and to become visible and to be slightly elevated if your parents or closest relatives - has the AD. Researchers have reconnoiter uncommon mutations in three genes that mostly guaranty an individual who receives them will progress disease. But these changes measure for lower than 5% of AD.

The Large amount of genetic mechanisms in AD in families stay undescribed. Apolipoprotein e4 (APoE4) is the strongest risk gene scientists have found, however, not all humans with this gene goes on to growth AD. Researchers identified other risk genes, but not conclusively supported.

c. Down Syndrome

Down syndrome in the people is risk to develop AD. Down syndrome is a cause to appear signs and symptoms of Alzheimer's and AD in patient with Down syndrome observed

10 to 20 years earlier in compared to people in usual folk. A gene included in the excess chromosome that made Down syndrome to significantly develop the risk of AD.

d. Gender

Usually AD more observed in women in versus to Man, because the live in women is longer.

e. Mild Cognitive Impairment

Remembering trouble or other signs of cognitive decline are present in patient with mild cognitive impairment (MCI) that are worse than able to anticipate for patient age, but not strongly sufficient to be analyzed as dementia.

Those with MCI have a developed risk but not a sure thing of later increasing dementia. Activity is case to expand a healthy and natural lifestyle and strategies to treat and cancel for decrease memory at this step may aid delay or prohibit the development of dementia.

f. Past Head Trauma

Usually persons with strong head damage in bygone, have more risk of Alzheimer's D.

g. Heart Health and Lifestyle

In generally there's no confirmed lifestyle factor that's been clearly proved to decrease your risk of AD. But, some acts declare that the alike causes that increase you involve to risk of heart disease also may develop or rise the chance that you'll take AD. For examples: Obesity, High blood cholesterol, High blood pressure, uncontrolled type 2 diabetes, Smoking or inhalation other pollutants, a diet without fruits and vegetables, Lack of exercise.

h. Lifelong Learning and Social Engagement

Researchers have reported a connection between long lives with activity in mentally and activity with friends and around people and a decrease risk of AD. Good and high education level (high school or more) also decrease of risk factor of AD (URL-1).

1.3.5. Complications

Failed judgment, remembering and damage or lack language, so information modifies produced by AD, therefore treatment for other health conditions are complicate. A patient with AD may be unable to: tell that she or he is having affliction, like, from a dental pain, report signs of another disease, and continue to prescribe plan for treatment, Notice or call about side effects of drugs and medication.

So that disease developed in its final steps, central nervous system modifies started to affect bodily activities, like bowel and bladder control, balance, and swallowing. These causes can develop easily to damage to extra health troubles like: Interring liquids or food into the respiratory system in inhaling time, Pneumonia and other diseases, Fractures, Bedsores, Falls, Malnutrition or dehydration (URL-1).

1.3.6. Pathophysiology of AD

a. Neuropathology

Decrease or loss of synapses and neurons in the cerebral cortex and other subcortical zones are characterizes of Alzheimer's disease. This decrease or lack effect on growth atrophy of the involved areas, contain new process in the temporal lobe and parietal lobe, and regions of the frontal cortex and cingulate gyrus. Decadence is also exist in brainstem nuclei like the locus coeruleus (Braak and Del, 2012). Scientists using PET and MRI have reported decrease in the volume of pointed brain areaes in people with AD as they progressed from mild cognitive damage to AD, and in collation with same images of fine health older adults (Desikan et al., 2009; Moan, 2009).

By use of microscope clearly observed amyloid plaques and neurofibrillary tangles in the central nervous system of those damaged by Alzheimer’s D (Tiraboschi et al., 2004). Plaques are thick and high concentration, largely not able to solution deposits of beta-amyloid peptide and cellular material out of neurons. Tangles are totally of the microtubule-associated protein tau which have converted hyperphosphorylated and collected within the cells themselves. However numerous older persons grow part of plaques and tangles as a result of old years, the brains of patient with AD have a larger amount of them in special brain parts

such as the temporal lobe (Bouras et al., 1994). Lewy bodies aren't scarce in the central nervous system of patients with Alzheimer's D (Kotzbauer et al., 2001).

b. Biochemistry

AD has been known as a protein amiss folding illness (proteopathy), make by plaque aggregation of unnaturally folded amyloid beta protein, and tau protein in the brain (Hashimoto et al., 2003). Plaques are produced of little peptides, 39-43 amino acids in tall, named amyloid beta (Aβ). Aβ is apart from the bigger amyloid precursor protein (APP). APP is a transmembrane protein that passes in the neuron's membrane. APP is important to neuronal development, post-injury repair, and survival (Priller et al., 2006; Turner et al., 2003). In Alzheimer's D, gamma secretase and beta secretase working with each other in a proteolytic procedure that rustles APP to be made shorter pieces (Hooper, 2005). One of these pieces gives growth to fibrils of amyloid beta, which then shape clamps that deposit out of neurons in thick made to recognize as senile plaques (Ohnishi and Takano, 2004).

AD is also deemed to be a tauopathy due to unnatural accumulation of the tau protein. All neurons have a cytoskeleton, an inner protection construction partially produced of complexes named microtubules. These microtubules work as tracks, molecules and food led by these microtubules from the body of the cell to the last parts of the axon and back. A protein knows as tau stabilizes the microtubules when phosphorylated, and is hence named a microtubule-associated protein. In Alzheimer's D, hyperphosphorylated becoming from undergoes chemical modifying, it then starts to make double with another threads, making neurofibrillary tangles and breakdown the neuron's transport system (Hernández et al., 2007).

1.3.7. Diagnosis and Techniques for Diagnosis of AD

Medical history of the person's usually is bases for diagnose AD, behavioral regards and history from family and other relatives. Exists of neuropsychological features and characteristic neurological and in the lack of periodic positions is patron (Mendez, 2006; Klafki et al., 2006). New and special medicinal pictures with magnetic resonance imaging (MRI) or computed tomography (CT), and with positron emission tomography (PET) or single-photon emission computed tomography (SPECT) can be used to aid bereave other brain trouble or other types of dementia. Furthermore, it may anticipation alteration from first

disease symptoms steps (mild cognitive impairment) to Alzheimer's disease (Schroeter et al., 2009).

Estimating of intellectual working including remembering examination can farther characterize the state of the illness (Waldemar et al., 2007). Medical arrangements have made finding scale to easy and standardize the distinction steps for exercising physicians. The distinctions can be accepted with richly precision post-mortem when central nervous system material is ready and present and can be tested histologically (McKhann et al., 1984).

AD Association established the most commonly used NINCDS-ADRDA Alzheimer's Criteria for diagnosis, last information reported by the Alzheimer's Disease and Related Disorders Association (ADRDA), and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) in 1984 (McKhann et al., 1984), in 2007 it was updated (Dubois et al., 2007). These system needed that the exits of cognitive damage, and a suspected dementia syndrome, be corroborated by neuropsychological examination for a medical identifications of probable or feasible Alzheimer's D. A histopathologic agreement contains a microscopic test of brain tissue is needed for a finally analysis and distinctions. Worthy mathematical validity and reliability have been presented between the finding scale and standard histopathological agreements (Blacker et al., 1994). Functional abilities, constructive abilities, orientation, language, perceptual skills, attention, problem solving and memory are 8 cognitive domains that usually damaged by Alzheimer's D. These domains are combining weight to the NINCDS-ADRDA Alzheimer's scales as ordered in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) reported by the American Psychiatric Association (American Psychiatric Association, 2000).

Neuropsychological examinations, for example the mini–mental state examination (MMSE) are to greet degree utilized to measure the cognitive damages necessary for identification. Much comparative exam arrays are needed for more validity of final obtains, especially in the first phases of the illness (Tombaugh and McIntyre, 1992; Pasquier, 1999). Neurological tests in new AD will commonly have normal results, without for obvious cognitive impairment, that they have the same results in all stages of disease, containing another types of dementia.

Farther neurological tests are important in the diversity finding of Alzheimer's D and another illness (Waldemar et al., 2007). Communication with close relatives and persons in family are so used in the estimating of the illness. Important or significant information can provided by caregivers on the daily living powers to continue, also on the reduce, over time, cerebral activity of the person's (Harvey et al., 2005). A caregiver's opinion is partially important, because people with Alzheimer's D is usually without information of his own defect (Antoine et al., 2004). Usually, peoples so have hard in the discovery of first dementia signs and may not connection correct knowledge to a doctor (Cruz et al., 2004).

Supplementary testing supplies more knowledge on any properties of the illness or is utilized to rule out other diagnoses. Blood exams can recognize another reasons for dementia than Alzheimer's D (Waldemar et al., 2007) reasons which may, in scarce samples, be revocable (Clarfield, 2003). It is public to accomplish thyroid activity tests, anemia, assess levels of heavy metals, rules out syphilis and assess B12, and rule out metabolic problems.

Psychological exams for distress are used, because depression can either be together with Alzheimer's D, one of the first signs of cognitive damage to change (Sun et al., 2008), or even the cause (Geldmacher, 1997; Potter and Steffens, 2007).

1.3.8. Treatment Strategies

Professional social attention to good health should all times search correct agreement from a person with dementia: This should include reporting the individual of choices and testing that patient to perceive, Testing so that there is no compulsion and that patient follow to agree in all time, If the someone misses the capacity to build a resolution, the preparation of the Mental Capacity Action 2005 must be pursued (Dementia: NICE Clinical Guideline, 2011).

a. Drug Treatment

New recently reviewed is presented by the National Institute for Health and Clinical Excellence (NICE), its guideline on the utilize these medicines in weak and temperate AD, take and carry it much in line with the Scottish Intercollegiate Guidelines Network (SIGN)

Before NICE guideline focused on the mini-mental state examination (MMSE) mark in distinguishing between mild (21-26), moderate (15-19), moderately severe (10-14) and severe (<10) AD when decision to remedy by Acetylcholinesterase (AChE) inhibitors.

SIGN also NICE to become apparent to accept that: The MMSE is not sensitive sufficient to distinguish ill who want useful of remedy for those who want not, and was not planned for this apply. Enforcement can be impacted by many causes, containing sagacity, power to speech English and with presence body illness at the time of doing the test. In some patient and from day to day happen minor variations. The total assessment of ill should contain MMSE, that containing social interaction and quality of life modifying. After this assessment, clinicians treating patients should be free, and should not be prevented from doing so on the base of the MMSE degree.

NICE recommendations: treatment by (AChE) inhibitor (galantamine, rivastigmine or donepezil) in patient with both types of AD (mild or moderate), should be considered. Only by dementia specialists (neurologists, psychiatrists, and physicians specializing in the care of older people), It should be started after a suitable discussion with cares and family members. These medicines should be started with low doses, because they have cholinergic side-effects, after that titrated depending patient reaction. Second-line is Memantine (a N-methyl-D-aspartate (NMDA) antagonist) suggested by NICE as a choice for managing ills with moderate AD where AChE inhibitors are not withstand or contra-indicated, or in the remedy of severe AD. Use of drug for treatment must be continued only as long as it is having a good result in functional or behavioral signs, cognitive, global. Ills on remedy should be checked in arranging time by an appropriate specialist team, or care used GPs where such an agreement presents. This should contain global, activity, and behavioral deliberation, cognitive and discussion with cares.

SIGN comments (Alzheimer Scotland; Action on Dementia) ACHE inhibitors must be noted in all patients with AD, irrespective of whether the dementia is mild, moderate or severe. Patients with mild-stage AD should be the best selection for treatment at the first chance after finding. This would able the ill to be complicated in determination about their care, and let more time for caring to be educated. It would be incorrect to keep out an ills from treatment after diagnosing of patient has been would be most likely to part high degrees of

ability than would be possible later in the disease. Getting price should be taken in measure, but should not over-ride other medical attention. Focusing on a remedy in the many on the steps of the disease could deter GPs from relating at a firstly step. Not all ills have prepared available to a specialist or specialist hospital, especially in peoples that lives out of cities. In these peoples, GPs should be permitted to start treatment (Dementia: NICE Clinical Guideline, 2011).

b. Alternative Medicine for Treat AD

Differences plant compounds, vitamins and other added components are largely supported as ready for formations that may protection cognitively healthy and inhibit or defer AD. Presently, not exist powerful document and formations from one of these medical gradually decrease the growing of cognitive.

Many of the remedies that have been new studied like: Omega-3 fatty acids. Omega-3 fatty acids in fish aid to stop or prevent cognitive decline. Researches done on fish oil with other added treat haven't shown any benefit, anyway. Curcumin. Has anti-inflammatory and antioxidant properties, this herb comes from turmeric and that strong affect chemical processes in the brain. In other side, clinical trials have reported no any help for treating Alzheimer's disease. Ginkgo. Ginkgo is a plant extract containing many of chemical compound. Many studies funded and reported by the NIH not find affect in stopping or treat AD. Vitamin E. Also, vitamin E is not memorable for inhibition AD, giving more than 2,000 international units every day can aid to reduce the improving in cases that presently have AD. Although, make a mix of results of the study, the mix only contains studies with beneficial results. Before studying within the health of more than 2,000 international units per day of Vitamin E in a dementia group will be necessary before it can be daily recommended.

Component supported for cognitive harmless can interact with the medical treatment you're giving for AD or other diseases. To make a remedial plan that true and good for you, is necessary to closely work with your care team. Make sure you perceive the harms and safes of all things it includes (URL-1).

c. Caregiver Burden

The demanding emotional and physical for patient with AD is caregiver burden. In before condition, worry and grief, stress and discouragement, feeling of angry and guilt, and social separation are public and common.

Caregiving can even receive a tax on the caregiver's bodily safety. But giving care to your self-needs and well-being is one of the more important matters you can do for yourself and for the patient with AD.

Some important things for you like a caregiver in more professional care health for patient with AD are: take information as in high degree about the illness, give help from doctors by asking questions, social workers and another affected in the care of your loved one, when you need help you can take it from friends, family and other close relatives, using a rest daily, consuming time with your closely persons, taking care of your health by visit your own physicians on program, getting sport activity and eating healthy foods, interring to a support teams, making utilize of a local adult day center, if you have ability to do those.

Most of patient with AD and their relatives useful from communication or local support assists. Connection your local AD society joining with protection teams, doctors, home care delegations, and educational seminars, occupational therapists, referrals and resources, residential care facilities, a telephone help line (URL-1).

1.4. Medicinal Plants

Medicine is the study and activity of the identification, remedy, and inhibition of illness ("Medicine". Oxford Dictionaries Online, 2014). The Latin Medicus that meaning "a physician" is a source for word medicine. Medicine contain a different of health nursing activity to keep and reparation health by the inhibition and remedy of disease. Medicine today uses biomedical study, biomedical sciences, genetics, medical technology to find, inhibit damage and illness and remedy, generally by an operation or pharmaceuticals, but also by medical cares as given as psychotherapy, medical devices, biologics, and ionizing radiation, external splints and traction, amongst others.

Plants that have Medicinal properties have been discovered and confirmed to utilize a long history of populations. To produce a different type of chemical complexes that utilized to

do special and basically biological activities are from characteristics of plants (Atanasov et al., 2015), and to prevent opposing attack by rapacious like dangerous animals and herbivorous, fungi and insects. Until today more than 12,000 chemical compounds have been isolated, estimated all this amount is only 10% of total compounds exist in the plants (Lai and Roy, 2004). Chemical complexes in medicinal herbs their act on the physical human through procedures similar to those yet good understood for the chemical complexes in remedies used today; thus medicinal plants do not more different from daily drugs in meanings of how they act. This plant medicine has ability to useful pharmacology, but also gives them the same properties to conventional pharmaceutical drugs to make harmful side effects (Lai and Roy, 2004).

In 2001, scientists founded 122 chemical compounds used in new medical science, which were taken from "ethnomedical" herb origins; 80% of those have had an ethnomedicine utilize similar or dependent on the present use of the chemical compounds of the herb (Fabricant and Farnsworth, 2001). Many drugs that currently present to medicine are taken of herbals that used like medical plants have a long history. Examples of such drugs like opium, aspirin, quinine, and digoxin (Swain and Tony, 1968).

For treat illness the use of plants is usually common in populations with non-industrialized, and is frequently most affordable than buying new drugs (Edgar et al., 2002). Use of medicinal plant is very common in both Asian and African countries, the World Health Organization(WHO) reported that 80% of these use medicinal plant in the initial stages of health care. Researches in the European and U.S. have reported that they utilize is low public in clinical settings, but has become elevated more public in the last years as scientific documents about the effectiveness of medicinal plant has become most vastly present. The yearly global transport value of pharmaceutical herbs in 2011 measured for more than US$2.2 billion.

Roots, flowers, leaves, seeds, berries, bark of medicinal plants has used in medicinal purposes.

1.4.1. Modern Studies of Plant Medicine

Many plants that have a long history of use like treatment, currently present as chemical compounds or drug to medicine, for example quinine, digitalis, opium and aspirin.

Buying of Pharmaceuticals is realy more expensive for large amount of people in world's societies, that about 50% of their lives on lower than $2 U.S. daily (Edgar et al., 2002).

In last years use and search in plants for extraction and finding of food and drug supplements are accelerated. Botanists, microbiologists, pharmacologists, and natural-products chemists are combination the Earth for phytochemicals and results that could be increased to treat different illnesses. Though, the World Health Organization reported, about 25% of new remedies used in the U.S. have been taken from herbals.

Approximately the 120 active chemical compounds basically taken from the herbs and generally used in new medicine now, 80% declare a positive relation between their new remedial utilize and the classic and old use of the herbals from which they are extracted (Fabricant and Farnsworth, 2001). About 35,000 that its equal to 2/3 of the plant species in the world estimated have medical properties that, coming from the industrial countries. Also about 7,000 chemical compounds used in the new remedies are obtained from herbs. In a large number of medicinal and aromatic plants (MAPs), significant alterations of herbs specifications have been determined and proved with changing soil characteristics, and the elective improving and subsequent release in viand of given elements have been proven. Main and big attention should be paid to select soil and agriculture output strategies, to acquire satisfactory crops of best quality and high costed crops, concerning their health and nourishing quality (Carrubba and Scalenghe, 2012).

1.4.2. Plant Chemical Compounds

Phytochemistry is the research about phytochemicals, which are chemicals taken from plants. Specifically, phytochemistry identifies the big number of secondary metabolic compounds found in plants. Most of these are known to make protection against insect and parasite attacks and plant illness. They also provide a number of protective activities for human users (John et al., 2013). Or make chemical compounds in all herbals as a function of their usual metabolic works. The phytochemical products in plants are distinguished into first-like fats and sugars that are present in all herbs and called primary metabolites; and second-other products that present in a lesser number and used for special functions in herbs are secondary metabolites (Meskin and Mark, 2002). For example, some of the second part (secondary metabolites) are pheromones used to attracting insects for pollination and other

parts are poisonous used to frighten enemies. It is these secondary metabolites and pigments and able to have remedial functions in men and that can be used to make drugs, such as digoxin from the foxglove, morphine and codeine from the poppy, inulin from the roots of dahlias, and quinine from the cinchona (Meskin and Mark, 2002). Toxic plants, even have use of pharmaceutical growth (Stepp and John, 2004).

A bewildering diversity of phytochemicals is produced by plants, but most are extracted of a little biochemical origin (Springbob et al., 2009). A bewildering diversity of phytochemicals is produced by plants, but most are extracted of a little biochemical origin. Alkaloids, Phenols or Polyphenols, Glycosides, Flavonoids, saponins , Terpenes are the most common phytochemicals produced as secondary metabolites in plants generally. We used essential oils for this study that mostly consist terpenes.

1.4.2.1. Terpens (Essential Oils)

Terpens produced by the high number of plants, and are different and a big class of organic compounds, for example conifers, that usually have strong smelling and thus may have had a keeper activity. Terpenes make the larger parts of resin, and the terpene type of resin is turpentine. (The term "terpene" is coming from the term "turpentine"). Terpenes are bigger biosynthetic building blocks almost in all living organisms. Such as steroids, are extracted of the triterpene squalene. When terpenes are changed chemically, for example by rearrangement of the carbon skeleton or oxidation, the terpenoids are the resulting compounds. Terpenoids and terpenes are the primary organizer of the essential oils of most kinds of herbals.Extracted essential oils widely used in traditional and alternative medicines such as aromatherapy, natural flavor additives for food, and as fragrances in perfumery. Produce altered and extracts of natural terpenoids and terpenes also expand in the world the, different of aromas used in flavors and perfumery added to foods. The examples for terpene are he carotenoids make the reds, oranges and yellows of tomatoes, pumpkin and corn, Vitamin A, and the fragrance of rose and lavender is due to monoterpenes.

1.5. *Hypericum* L. Genus

Genus *Hypericum* contain 490 flowering plant species within the family Hypericaceae (some time counted a subfamily of Clusiaceae) (URL-2). *Hypericum* is uncommon for a genus

of its size because a global classification monograph (URL-2) was N. Robson made it for *Hypericum* (hi working in London, UK, at the Natural History Museum, from 1977 to 2012). Robson found and distinguished 36 subdivisions inside *Hypericum*. The *Hypericum* has an almost found it in all around of the world, lost only from deserts and polar regions and equatorial low level lands. All plants of the genus may be related to as St. John's wort, though they are also publicly named *Hypericum*.

Hypericums have very different from perennials or herbaceous annual that have 5 to 10 cm tall for shrubs and about 12 m tall for trees. Arrangement of leaves is opposite to each other, oval simple, 1–8 cm tall, they are both forms of evergreen or deciduous. The color of flowers is very different from dark yellow to pale, with diameter between 0.5 to 6 cm, mostly contain five petals (four petals is rare), stamens are prominent in most species. The crop is commonly a dry capsule which splits to distribute the high number of tiny seeds; in the part of *Hypericum* it is fleshy and berry-like (Fine Gardening, 2015).

Numerous species of *Hypericum* with large and showy flowers used like ornamental herbs. Some hybrids and cultivars have been expanded in new generation for use in scientific gardening. St. John's-worts can happen as harm weeds in farming areas and gardens. On grassland, many of them can be larger than a harm, sometimes abortion in livestock and origination for make weak photosensitivity. A species of moth use *Hypericum* species are the only known source food plants of the larva of the Treble-bar. Some of Lepidoptera species whose larvae sometimes give food to *Hypericum* include Common Emerald.

Herbalism used Common St. John's-wort for a long time. It had information that Hypericum have medical specificities in Classical Antiquity and was a standard ingredient of theriacs, from the Mithridate of Aulus Cornelius Celsus' De Medicina (ca. 30 CE) to the Venice treacle of d'Amsterdammer Apotheek in 1686. Different shapes of usage people of *Hypericum* include oily extract ("St. John's oil") and snaps (Fine Gardening, 2015). Many of *Hypericum* species having the very strong species and it is now developing commercially used to make drug and medicine (USDA.gov, 2015); another St. John's-worts have attractive specifications and chemical compounds but are not well founded. As these secondary products showed to be depended to prevent herbivores and enemies, they are existing in altering and unpredictable quantities: yet, the amount of high-yield cultivars have been elevated.

Both hyperforin and hypericin are counted to have antibiotic characteristics (Samadi et al., 2010). Justify this opinion with the then progress philosophy of signatures, William Coles that he was an herbalist from1626 to 1662 reported in the 17th century that "The small gaps where the leaves of Saint Johns wort are full, doe appear like all the holes in the skin and therefore it is useful for all hurts and lesions that can take place thereunto" (Coles and William, 1657).

Extracted from *Hypericum*, by stimulating both the CYP3A4 and the P-glycoprotein, can increase the plasma collections of various anticancer agents such as imatinib (a drug used to treat certain types of cancer), irinotecan and docetaxel, thus decreasing the clinical effectiveness of these medicines (Caraci et al., 2011).

1.5.1. *Hypericum scabrum* L.

Hypericum scabrum L. has also been used in traditional medicine for a long time, especially in Turkey (Barnes et al., 2001; Kizil et al., 2008; Ozen & Bashan, 2003; Pu et al., 2009). There are some reports about the Extraction Oil (EO) compositions of this plant from Turkey, Uzbekistan and north of Iran (Javidnia et al., 2008). The major component in the EOs of these plants was α-pinene with an average of about 45% to 50% (Fig. 1).

(A) (B)

Figure 1. *Hypericum scabrum* picture: A- dried sample, B- Plant in nature

H. perforatum L. and *H. scabrum* L. are both utilized in fighting different infections lead to their anti-inflammatory, antioxidant, antimicrobial and cicatrizing properties. Their oils contained high amounts of mono and sesqui-terpenes.

From the antioxidant view point, information about different extracts of *H. perforatum* and *H. scabrum* have been reported (Ayan et al., 2007). In these reports, polar extracts such as methanol, ethanol and hydro alcoholic extracts show various antioxidant activities measured by different methods; some bioactive compounds, especially from *H. perforatum*, are also known and their antioxidant activity has been shown (Zuhal, 2009). However, information about antioxidant activity of EOs from these plants is very limited.

EO from *H. scabrum* has also shown a broad spectrum of antibacterial activities and against *S. aureus*, it is reported to be more effective than the standard antibiotics such as ampicillin/sulbatam.

Although there are many research works in the literature on the biological activities and the composition of EOs of different *Hypericum* species, very few of them address biological properties of their EOs (Kizil et al., 2008). The limited information on the volatile chemistry or biology of this genus is thought to be due to low yield of EOs obtained from general extraction methods such as hydro-distillation (Gioti et al., 2009).

1.6. The Aims of the Study

The main purpose of this study is to evaluate the possible neuroprotective activities of *Hypericum scabrum* essential oil in scopolamine- treated rats. To reach this purpose a number of tests will also be carried out in this study. These include the analysis of chemical composition of the *H. scabrum* essential oil and to determine the possible effects of *H. scabrum* on spatial memory by using Y-maze task and radial arm-maze task, as well as antidepresant activity in forced swimming test. The anxiolytic activity also was measured in elevated plus maze. The determination of Hippocampal and Amygdala GPX (glutathione peroxidase), GSH (glutathione) and SOD (superoxide dismutase) activity were carried out in this study. We also calculated MDA (malondialdehyde) level as biochemical parameters to learn antioxidant activity. The possible effect of the essential oil on oxidative stress in scopolamine –induced rats will also be evaluated.

2. MATERIALS AND METHODS

2.1. Plant Materials

Hypericum scabrum was collected during the flowering period in jone in Elazig, Eastern Anatolia, Turkey. The examples of the herbals are to be identified and prepared by herbarium material and stored in the Firat University Herbarium (FUH) in Biology department.

2.2. Essential Oil Extraction

All parts of the plant except root and a few portions of the stem within soil (aerial parts), dried in shadow, then broken into small parts, and by using a Clevenger-type apparatus and hydro-distillation (In this method, the parts of plant are heated, by steam that between plant parts or by putting it in boiling water. The result of steam and healing is a cause to break burst the cell structure of the herb parts, finally the essential oils extracted. The steam of boiled water carried essential oil molecules through pipe and channel with a cooling pool, after return to the liquid shape and are accumulated in where they return to the liquid form and are collected in a curved part of the apparatus. The liquid is a complex of water and oil, since not water soluble essential oils, separated and usually lighter collected on the surface of water in the vat, the next step is separately siphoned water and oil off (Zainal et al., 2015)) for 3 hours the oil was extracted (Fig. 2).

Figure 2. Clevenger-type apparatus.

2.3. Chromatographies Analyses of Essential Oil

2.3.1. GC- FID (Gas Chromatography/Flam Ionization Detector) Analyses

GC-FID (Agilent 6890 GC) is an instrumental way to analyse of Essential oils. We used GC- FID for the analysing of the essential oils and quantification of the chemical composition of the oils. This instrument contains a column of HP-5 MS (30 m × 0.25 mm i.d., film thickness, 0.25 μm) and sensor or tracer in Plant Products and Biotechnology Research Laboratory (BUBAL), Firat University(Fig. 3).

2.3.2. GC- MS (Gas Cromatography/Mass Spectrometary) ANALYSES

For identify different materials in sample that used for tests usually Gas chromatography–mass spectrometry (GC-MS) is used. Also GC-MS uses contain environmental analysis, identification of unknown samples, drug detection, explosives investigation, fire investigation, and containinig that of part samples taken of herb.

The plant oil or other samples were entered by splitting and the divided or separate and relation is 1:100. The oven heat degree of GC is protected at 70°C for 120 seconds and planned to 150°C at a range of 10°C/min and then protected stable at 150°C for 15 minutes to 240°C at a range of 5°C/min. For carrier gas used Helium in a flow range of 1 ml/min. Taken MS at 70 eV (Electronvolt) and a mass rate of 35-425. Comparison of their retention times (RT), their retention indices (RI) and mass spectra with those taken from reliable Wiley libraries (available through Hewlett Packard) and the literature are the parameters to recognition of the mixtures (Adams, 2007).

Figure 3. GC-FID / MS In plant Products and Biotechnology Res. Lab.

2.4. Animals Modelling

42 female Wistar ranges (albino) weighing from 200 to 300 grams at the beginning of the scientific research was used. Use of rodent for this experiment depended to; rodent and especially mice and rats depended to the Euarchontoglires clade that contains men. This nearly relationship, the make high homology connected with humans, their ease of keeping activity in good working and handling, and their large produce new generation and reproduction ratio, makes rat especially fit and good models for human-oriented study. The research lab rodent genome has been sequenced and many mice and rat genes have human homologs.

The rats are kept in laboratory condition in a special heat degree (22°C) and light in the laboratory (a 12-h cycle beginning at 10:00 hour) and let them taken water food. Divided all 42 rats into 6 sets or groups and 7 rats per each set (Fig. 4): first group; Control group taken 0.9% saline with 1% Tween 20 treatment; second group; Scopolamine (Sco.) - alone-treated group, as negative control and obtained 0.9% saline with 1% Tween 20 treatment; third group; Diazepam alone-treated group (DZP, 1.5 mg/kg) as positive control and obtained 0.9% saline with 1% Tween 20 treatment; fourth group; Tramadol alone treated group (TRM, 10 mg/kg) as positive control and taken 0.9% saline with 1% Tween 20 treatment; fifth group; Scopolamine-treated group received *H. Scabrum* essential oil 1% (Sco.+HEO1%) and sixth group; Scopolamine-treated group received *H. scabrum* essential oil 3% (Sco.+HEO3%). Control, Diazepam, Tramadol and scopolamine alone-treated groups were put in cages in the similar situations but without of the experienced essential oil. They were topical to inhale 0.9% saline with 1% Tween 20 solution. Animals are treated in conformity with the program of the animal bioethics of the Action on Animal Experimentation and Animal Health and Welfare from Turkey and all routine and process were in conformity with Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 for the support of animals utilized for scientific researches and works.

Figure 4. Laboratory rats

2.5. Inhalation and Drug Treatment

A special apparatus that used for inhaling evaporated oil consists of a Plexiglas box with cover (0.5 m x 0.4 m x 0.28 m) (Fig. 5). Two boxes were utilized, one of the first group (control) and a second group (scopolamine alone-treated) rats that were inhaled 0.9% saline with 1% Tween 20 solution, also second box used for rats in 1%, 3%, DZP and TRM groups, which were inhaled *H. scabrum* (1% and 3%) essential oil. *H. scabrum* extracted oil was reduced concentration by 1% Tween 20 (v/v). *H. scabrum* essential oil used (0.2 ml, either 1 percent or 3 percent) was per an electronic instrument for evaporation (Oregon Scientific WS113), or manually by candle for sources of heat and candlestick like container for oil placed on the floor of the inhalation instrument, but kept of attainment of the rats. Respecting concentrations to be employed in the pharmacological experiments, we picked 1% essential oil usually utilized in aromatherapy and a high concentration (3%) in grade to accentuate the effects (Gradinariu et al., 2014). Animals in the *H. Scabrum* essential oil groups were put into inhaled oil for checking in 15 minutes, every day, for 21 nonstoped days. 10% ethanol used for cleaning boxes every day after tests. Negative control is scopolamine hydrobromide (Sigma-Aldrich, Germany) was used with an isotonic solution (0.9% NaCl) and 0.7 mg/kg scopolamine to make a solution, then was injected intraperitoneally (i.p.) to the rats, half of hour in front the behavioural testing. Positive controls are Diazepam (Sigma-Aldrich,

Germany) and Tramadol hydrochloride (Sigma-Aldrich, Germany) were injected intraperitoneally (i.p.) 1 ml/kg in rats, 1 hour in front of behavioral tests.

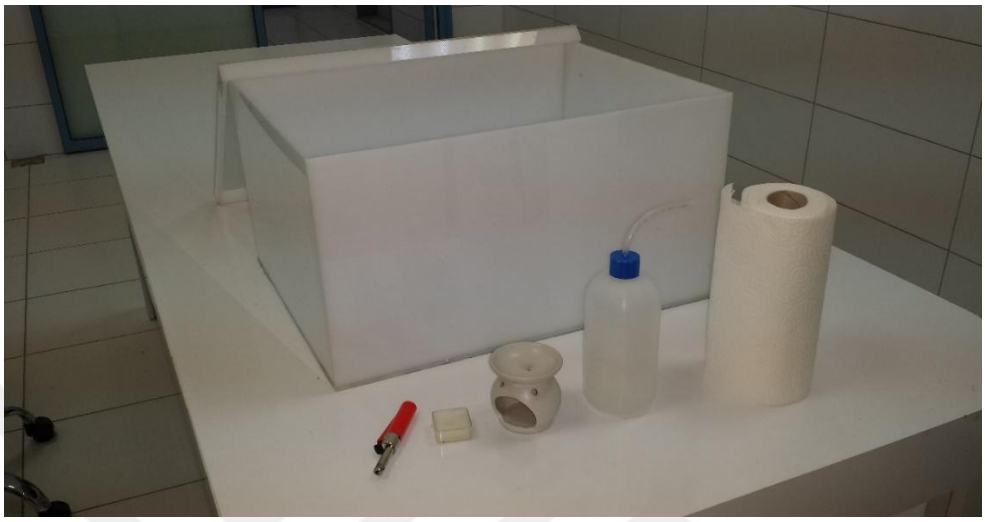


Figure 5. Inhalation apparatus

2.5.1. Y-maze Task

By spontaneous alternation behavior and used the Y-maze task, short-term memory was measured. In the present study the Y-maze task consists of an equilateral triangular in the central area and three limbs or arms (0.35 m long, 0.25 m high and 0.1 m wide) (Fig. 6). 15 minutes after the smoking of *H. scabrum* extracted essential oil (HYP1% and HYP3%), rats were put at the end of one of the three arms and let to walking within the instrument for 8 minutes in all directions. An entry to the arm is recorded when the all limbs (2 hands and 2 feet) of the rat were wholly inside the one arm. Spontaneous alternation behavior was described as in coming into all three arms on successively selected. The amount of higher number of spontaneous alternation behaviors was then the all amount of arms penetrated less 2 and percentages, spontaneous alternation was counted as (really alternations/maximum alternations) X 100 (Hritcu et al., 2014). Indicate spatial working memory that is a kind of short-term memory was considered by spontaneous alternation behavior,.

Figure 6. Y-maze task apparatus

2.5.2. Radial Arm-maze Test

The radial arm-maze apparatus was used in the existing research contained of eight limbs or arms, signed by numbers and the number of arms started from 1 to 8 (0.48 m length x 0.12 m wide), expanding from central area and radially arranged (0.32 m in diameter) (Fig. 7). For better result the apparatus was put 0.5 m to a higher place on the floor, and confined on all sides by a different extra-maze visible cues to remaining animals at the same limited place in the test time. Before the real or true training started, each group of rats were at the same time placed in the radial arm-maze apparatus and let them to search for 5 minutes and eat the food freely. The food at the beginning of the test was available in all arms and center of the maze, but was step by step or gradually closed to the food cup. The choice of the baited arms depends on the fact that rats, promote to solve the maze using a close and near arm selection strategy. In our test, we modified nearly arm shaping behavior by only feeding 5 arms (no 1, 2, 4, 5, and 7) objecting rats to modify their strategy and prevent the non fed arms. Each arm

measured entry when all four hands and feet of the animal were within an arm. Counts were made of the amount of working memory errors (entering an arm, including food, but formerly entered) and reference memory errors.

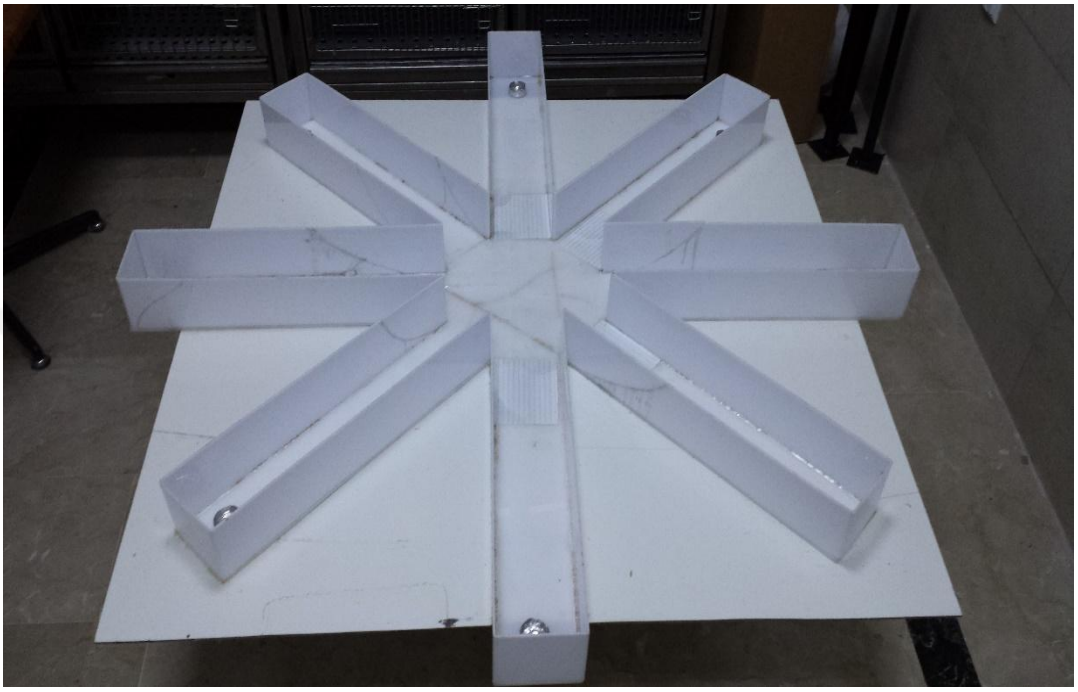


Figure 7. Radial arm-maze test apparatus

2.5.3. Elevated Plus-maze Test (EPM)

Behavior in EPM is also used to measure motor behavior, recognition and anxiety. This apparatus made of four branches, 0.49 m length and 0.1 m wide, raised 0.5 m up the floor (Fig. 8). Two arms were opened and not surrounded by walls and the other two arms were closed by 0.3 m high walls. Firstly, let the rats in each group to inspiration of *H. scabrum* extracted essential oil (HEO1% and HEO3%) for 15 minutes, then, one by one animals was put in the middle of the maze apparatus facing one closed arm. Behavior was looking for 5 minutes, and the time paid and number of entries into the open and enclosed arms was measured (Hayashi et al., 2012). The percentage of the time consumed in the open arms (time consumed in the open arms/time consumed in total arms x 100) is calculated. And, the all number of open- and enclosed-arm entries (number of crossing), that is the reason for the exploratory activation of rats (Rodgers and Dalvi, 1997), are counted. One intern is described

as a rat putting all limbs within an arm, so when the rat was in the central area recording of time was stopped.

Figure 8. Elevated plus-maze test apparatus

2.5.4. Forced Swimming Test (FST)

For measuring depressive-like response, the model Forced Swimming Test is used (Cryan et al., 2002). The depressive-like response was measured, basically using the same method delineated by Fernandes and Campos et al., 2005, but with some changes. On the pretest session or start day of the tests, subjected animals were one by one put into cylindrical recipients (diameter 0.3 m, height 0.59 m) including 0.25 m (usually depended to length of rats) of water at 25 to 27°C (Fig. 9). The rats were let to swim for 6 minutes before being taken out of the cylinder, dried and taken back to their cages. The process was successively after 24 hours (next day), within test session or 6 minute swim period, 15 minutes after the inspiration of *H. scabrum* extracted oil (HEO1% and HEO3%). During the test period, the following behavioral results were measured: firstly- time spent floating with the minimal movements to keep the head above the water and called immobility time; and second- time spent with active swimming movements and called swimming time.

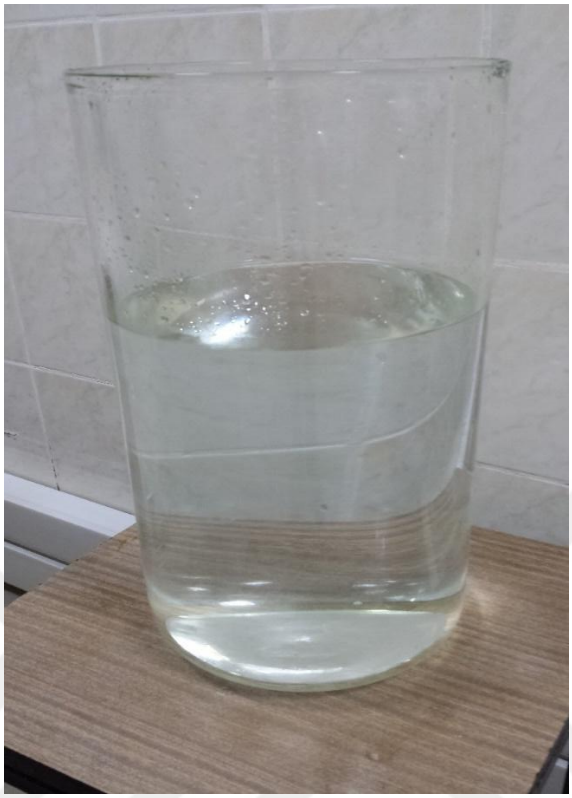


Figure 9. Forced swimming test apparatus

2.6. Biochemical Assays

After the behavioural experiments, all animals of 6 groups were stronger and completely anesthetized by using sodium pentobarbital, 100 mg/kg b.w., i.p.; Sigma-Aldrich and decapitated and wholly brains were dislodged. The both sides of the amygdala and hippocampus were carefully cut and separated (If the test could not be done immediately, store the sample under the temperature of -20℃ to prevent the repeated frost-thawing). Weigh the sample after cutting. Feed the certain amount of PBS, PH7.4. Use the liquid nitrogen for fast frost and for backup. After the thawing of sample, keep the temperature of 2-8°C. Feed the certain amount of PBS (PH7.4) and homogenate it manually or with homogenizer. Make cernterfugation for about 20 minutes (2000-3000 rpm). Collect the supernatant carefully. Separate it and use one piece for testing and frost the others for backup. The supernatant was used for tests of SOD and GPX-specific activities, the total content of decrease GSH levels (by ELISA).

MDA was analyzed by spectrophotometric method. For make buffer, 0.42 gr Tris-Base + 1.43 gr Tris-HCl + 3 gr KCl ve 0.5 ml Tween 20, 250 ml distilled water then mixed by magnetic hot shaker. 0.1 gr of tissue added to 1 ml of upper solution. Homogenized for 2 minutes. Centrifuged the solution at 5000 rpm for 4 minutes. Supernatant was used for assay of the all amount of decrease MDA levels.

2.6.1. Determination of Hippocampal and Amygdala GPX, GSH and SOD Activity

Glutathione peroxidase (GPX), Glutathione (GSH) and superoxide dismutase (SOD) activity was analyzed by a standard ELISA assay. Before the operation, balance the kit for half an hour under room temperature. Do not feed the blank well and feed only colored substrate A,B (TMB tetramethyl benzidine) and stop solution (2M H_2SO_4) for zero setting.

Standard well: feed the 50μl diluted standard in each well and feed 50μl standard/sample diluent (ultrapure water) in the zero well and then feed a 50μl working solution of biotinylated antigen. Sample well: feed 50μl sample (recommend to feed the sample directly and use the sample diluent for 2-5 times dilution if the concentration is high) and then feed a 50μl working solution of biotinylated antigen. Sway tenderly and cover the plate sealer and then incubate it in 37℃ incubator for 60min. Use distilled water for 25 times dilution of 25 times concentrated wash buffer (PBST containing 0.15% tween-20) for backup.

First washing: remove the plate sealer carefully and throw away the liquid and dry the plate to feed each well with wash buffer and then stand for 30 seconds before abandonment. Repeat the operation 5 times and dry it by clap. Feed the 50μl avidin-HRP in a standard well and sample well and sway it tenderly and cover the plate sealer and then incubate it in 37℃ incubator for 60minutes.

Second washing: remove the plate sealer carefully and throw away the liquid and dry the plate to feed each well with wash buffer and then stand for 30 seconds before abandonment. Repeat the operation 5 times and dry it by clap.

Coloration: feed 50μl colored substrate A in each well and then feed 50μl colored substrate B. Sway and mix it tenderly and keep away from light for 10 minutes for coloration. Stopping: feed 50μl stop solution in each well to stop the reaction (the color changes from blue to yellow)

Measurement: use blank well for zero setting and measure the absorbance (OD value) of each well under 450nm wavelength. Make measurable within 10 minutes after feeding the stop solution. Calculation: calculate the regression equation of standard curve according to concentration and OD value. Recommend to use the special software for calculation. ELISAcalc is recommended. Choose logistic curve (four parameters).

2.6.2. Determination of Hippocampal andAmygdala MDA Level

Spectrophotometer was used to record the amount of malondialdehyde (MDA), that is a signal of lipid peroxidation, by using the thiobarbituric acid examination as formerly delineated by (Ohkawa et al., 1979). 2 ml of supernatant was put and quickly combined with 1 ml of 50 % trichloroacetic acid in 0.1 ml HCl and 1 ml of 26 mM thiobarbituric acid. Than combined with magnetic mixing, solutions were stored at 95 ˚C for 120 minutes. Next, samples were centrifuged at 5000 rpm for 5 minutes and supernatants were read at 532 nm (ABS number + 0.0344) / 0.0492 * 10. A gradation curve was made using MDA as standard and the results were explained as nmol/mg protein.

2.7. Statistical Analysis

Behavioural results in the Y-maze task, EPM and FST and biochemical assays were analyzed by one-way analysis of variance (ANOVA) applied by Tukey post hoc test using GraphPad Prism 6 or GraphPad Prism 7 software for Windows, and radial arm-maze test using XLSTAT software for windows. In arrangement to assessment, modification between groups in the RAM task, separate repeated measures ANOVA was measured on the amount of reference memory errors and the amount of working memory errors with a group (Control, Sco., Sco. + HEO1% and Sco. + HEO3%) as between-subject factor and first day to seventh day as within-subjects causes. All conclusions are shown as mean ± standard error of mean (S.E.M). F values for which $p<0.05$ were observed as statistically significant. Significant differences were resolved by Tukey's post hoc test. Pearson's relation coefficient and retrogression analysis were utilized in arranging to measure the correlation between behavioural calculates, the antioxidant defense and lipid peroxidation.

3. RESULTS

3.1. Chemical Compounds of the *Hypericum Scabrum* Essential Oil

The main chemical compounds of the *H. scabrum* essential oil was analyzed by GC–FID/MS (Gas Chromatography/Flam Ionization Detector/Mass Spectrometry) (Tab. 3.1). The whole amount of 68 various compounds was separated which constituted 95.2 % (w/w) of the total extracted essential oil. The important and fundamental compounds of the essential oil were monoterpene hydrocarbons (C10H16), contain α-pinene (51.3 %), β-pinene (7.7 %), and Spathulenol (3.4 %), that measured for 62.4 % of the total extracted essential oil.

Table. 1. List of chemical composition of *Hypericum scabrum*

NO	Constituents	RI (Retention Index)	Concentration (%)
1	Nonane	995	1.6
2	α- Thujene	1015	0.9
3	**α-Pinene**	**1024**	**51.3**
4	α- Fenchene	1033	0.1
5	Camphene	1034	0.4
6	**β-Pinene**	**1055**	**7.7**
7	Sulcatone	1060	0.1
8	β- Myrcene	1064	2.4
9	α-Phellandrene	1076	0.1
10	Δ-3- carene	1078	0.1
11	α-Terpinene	1085	0.1
12	o-cymene	1091	3.0
13	Dl-Limonene	1094	2.0
14	β-Phellandrene	1096	0.3
15	β –trans ocimene	1099	0.1
16	Cis-ocimene	1107	1.5
17	γ- Terpinene	1116	0.5
18	α –Terpinolene	1136	0.2
19	Isopropenyltoluene	1140	0.1
20	Undecane	1147	1.4
21	Fenchol	1162	0.1
22	α- Campholenal	1167	0.2
23	Trans-pinocarveol	1177	0.1
24	Trans-Verbenol	1180	0.2
25	Borneol	1199	0.1
26	4-Terpineol	1204	0.2
27	M mentha 2,8 diene	1215	0.7
28	D-Verbenone	1223	0.1
29	Carvacrol	1295	0.1

30	α –Cubebene	1335	0.1
31	α- Longipinene	1338	0.1
32	Ylangene	1353	0.1
33	α-Copaene	1358	0.4
34	β –Bourbenene	1365	0.2
35	β-Elemene	1369	0.1
36	α-Gurjunene	1382	0.1
37	β –Caryophyllene	1392	1.5
38	β –Cubebene	1399	0.2
39	Aromadendrene	1405	0.3
40	β –Farnesene	1414	0.1
41	α-Humulene	1416	0.1
42	Neoalloocimene	1420	0.1
43	γ- Cadinene	1429	1.7
44	Germacrene-D	1434	1.2
45	4,11-selinadiene	1436	0.1
46	β –Selinene	1439	0.3
47	γ- Muurolene	1441	0.5
48	α-Selinene	1444	0.3
49	α-Muurolene	1445	0.2
50	α-Farnesene	1448	0.1
51	α-Amorphene	1454	0.7
52	Δ –Cadinene	1457	1.1
53	L-Calamenene	1459	0.4
54	α-Cadinene	1469	0.2
55	α-Calacorene	1472	0.2
56	Dodecanoic acid	1485	0.5
57	**Spathulenol**	**1494**	**3.4**
58	Caryophyllene oxide	1497	1.1
59	γ-Gurjunene	1499	0.2
60	Isospathulenol	1525	0.3
61	γ-Selinene	1533	0.3
62	α-Cadinol	1538	0.7
63	12-Norcyercene-B	1557	0.5
64	Hexa hydro formyl acetone	1630	0.2
65	n-Hexadecanoic acid	1692	1.0
66	Phytol	1791	0.4
67	9,12,15-octadecatriene-1-ol [ZZZ]	1809	0.4
68	Tricosane	1900	0.1
	TOTAL		**95,2**

3.2. Detection Spatial Memory in Y-maze Task Effected by *Hypericum Scabrum* Essential Oil

For analysis of spatial working memory in Y-maze task we used the one-way ANOVA. This program used to detect important or significant differences between all groups ($F(3.12) = 8.926$, $p<0.005$) that documented by the spontaneous alternations %. The Tukey's post hoc analysis to detect significant differences between the control group vs. Scopolamine group ($p<0.001$), Scopolamine group vs. Sco. +HEO1% group ($p<0.01$) and Scopolamine group vs. Sco. +HEO3% group ($p<0.01$) for the spontaneous alternations percentage (Fig. 10).

Nonsignificant differences between the scopolamine treated-group rats, exposure to HEO1% and HEO3% of the number of arm entries were noticed.

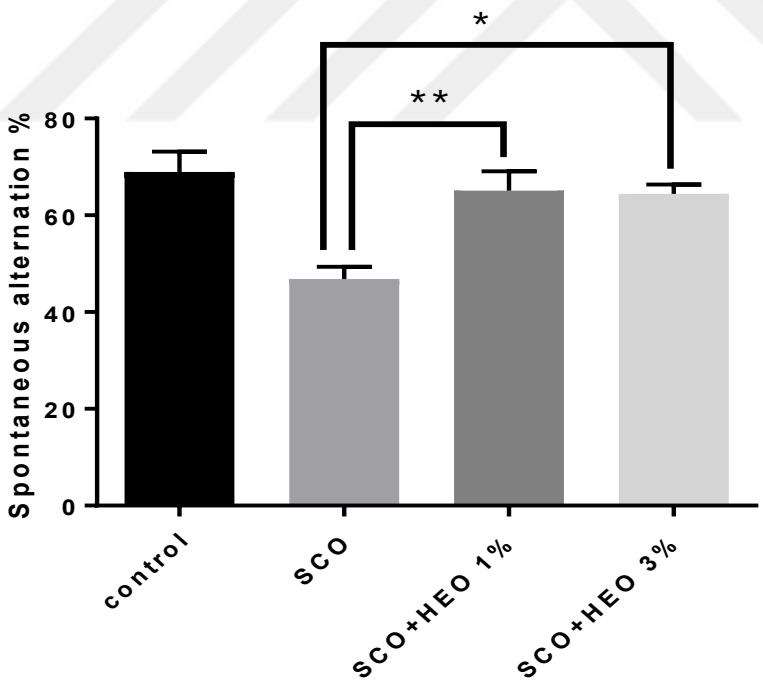
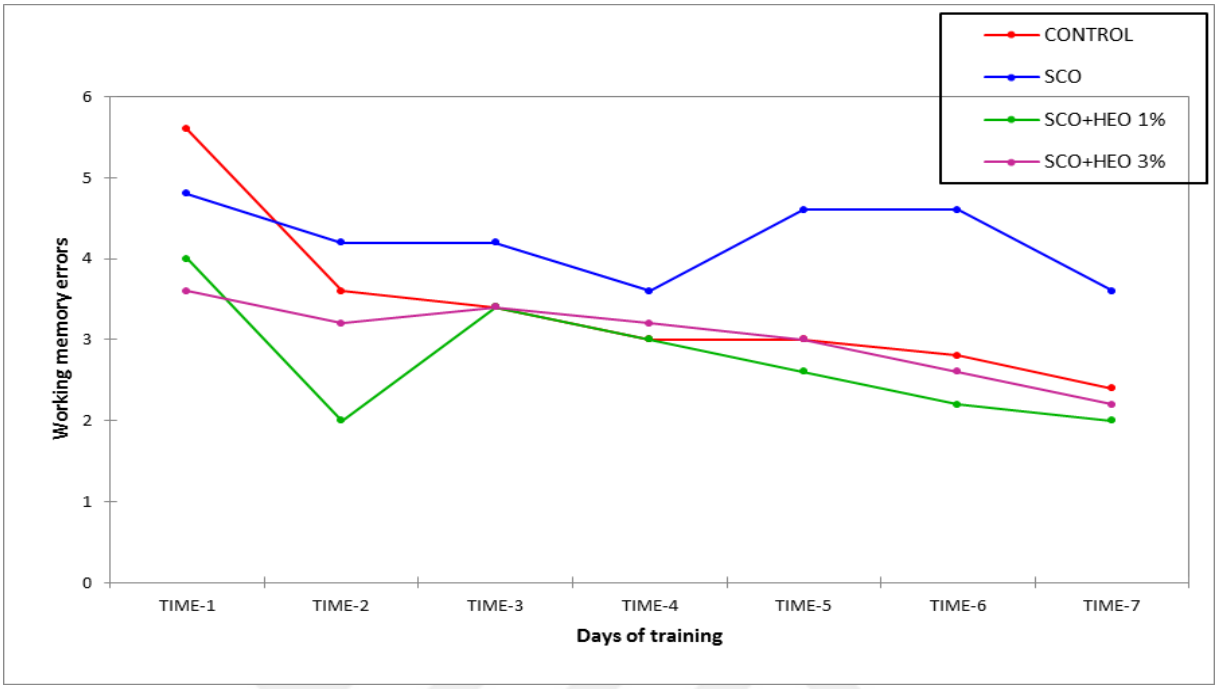


Figure 10. Effect of inspired *Hypericum scabrum* essential oil (HEO1% and HEO3%) in the Y-maze task on spontaneous alternation %, in the scopolamine (Sco.)-treated rats.

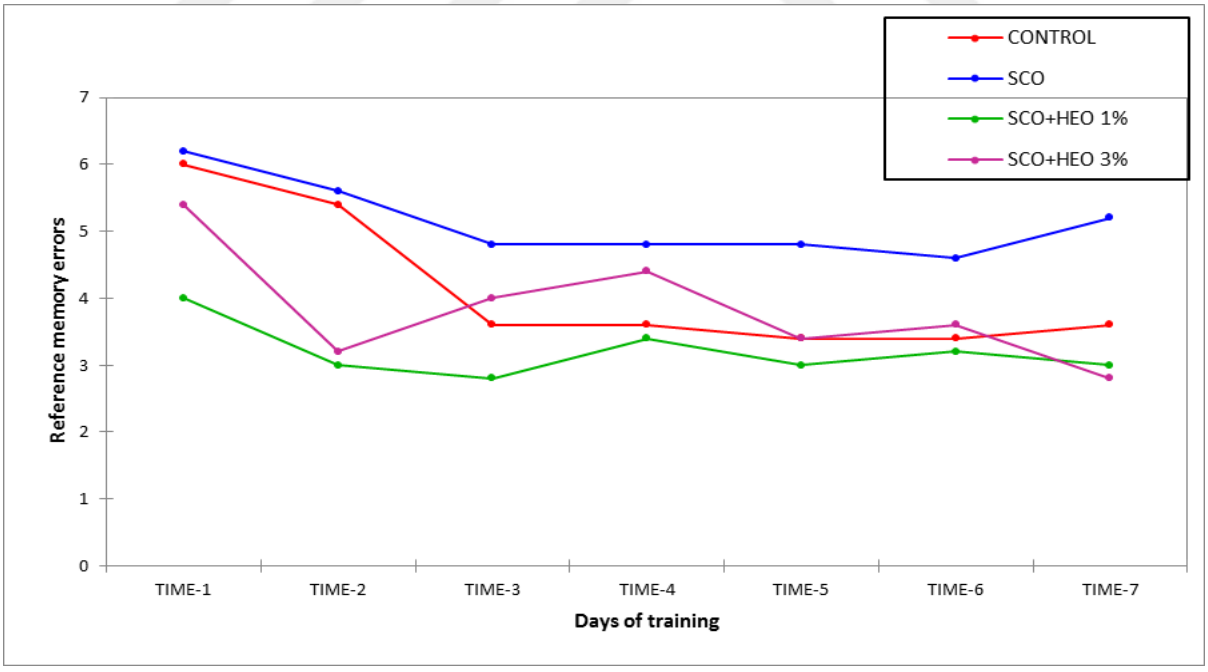
3.3. Detection Special Memory in Radial Arm-maze Task Effected by *Hypericum scabrum* Extracted Essential Oil

To analyze the take or inhalation of the *H. scabrum* essential oil impressions the spatial memory formation, the rodents were farther measured in the radial arm-maze task.

Repeated-measures ANOVA to detect a significant time difference ($F(6,112) = 2.569$, $p<0.05$) and a significant rat group difference ($F(3,112) = 4.454$, $p<0.005$) for working memory errors (Fig. 11 a.). Furthermore, repeated measures ANOVA to detect a significant time difference ($F(6,112) = 2.922$, $p<0.01$) for reference memory errors (Fig. 11 b.).



a.



b.

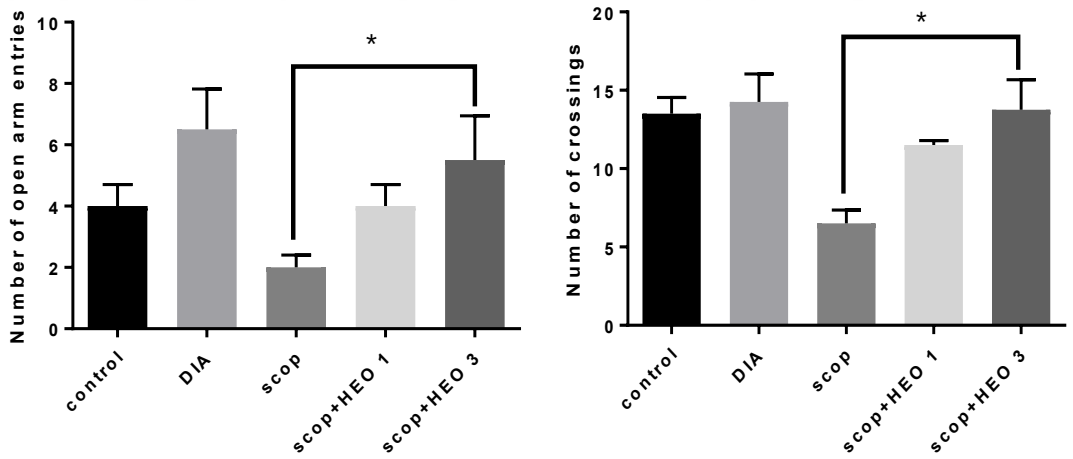
Figure 11. Effects of inhaled *Hypericum scabrum* essential oil (HEO1% and HEO3%) during 7 days training on the working memory errors (a) and the reference memory errors (b) in the radial arm-maze test.

3.4. Detection Anxiety in Elevated Plus-maze Test (EPM) Effected by *Hypericum Scabrum* Essential Oil

For analysis of anxiety in Elevated Plus-maze Test we used the one-way ANOVA.

In the EPM task ANOVA to detect a significant all over effect ($F(4,15) = 2.925$, $P<0.05$) on the number of open-arm entries. And, Tukey's post hoc analysis exposed a significant difference between DIAZ group vs. Scopolamine group ($P<0.05$) and Scopolamine group vs. Sco. +HEO3% group ($P<0.05$) for the number of open-arm entries (Fig. 12 a.).

In the elevated plus-maze task ANOVA to detect a significant all over effect ($F(4,15) = 5.750$, $P<0.005$) on the number of arms crossings. And, Tukey's post hoc analysis exposed a significant difference between control group vs. Scopolamine group ($P<0.01$), DIAZ group vs. Scopolamine group ($P<0.005$) and Scopolamine vs. Sco. +HEO3% group ($P<0.01$) for the number of arm crossings (Fig. 12 b.).



a. b.

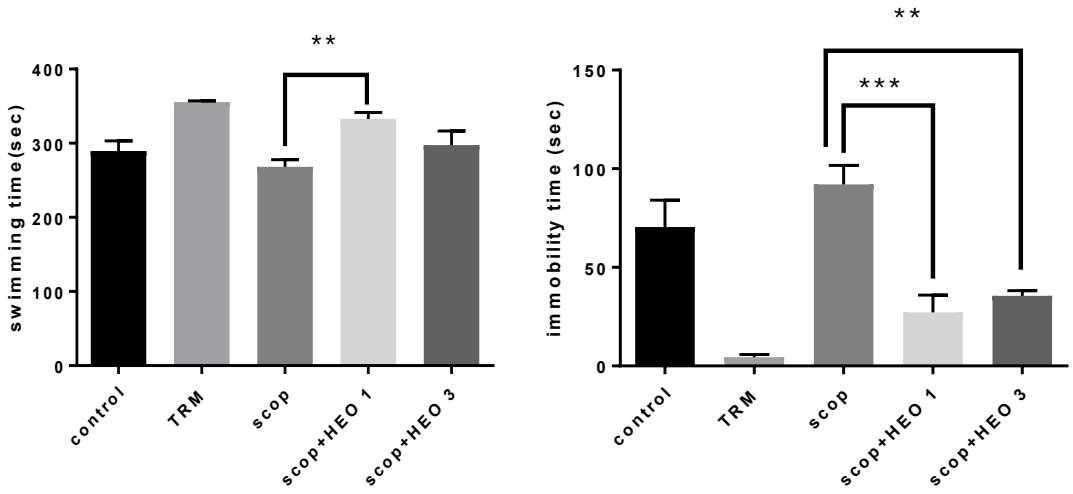
Figure 12. Effects of the inhaled *Hypericum scabrum* essential oil (HEO1% and HEO3%) in the elevated plus-maze test, in the scopolamine (Sco.)-treated rats, a. Number of open-arm entries, b. Number of crossings.

3.5. Detection Depression in Forced Swimming Test (FST) Effected by *Hypericum Scabrum* Essential Oil

For analyses depression in Forced Swimming Test we used the one-way ANOVA.

In the FST, ANOVA to detect a significant all over effect on the swimming time ($F(4,20) = 8.566$, $P<0.001$) and on the immobility time ($F(4,20) = 16.75$, $P < 0.0001$]). And, Tukey's post hoc analysis to detect a significant difference between control group vs. TRM group ($P<0.01$), TRM group vs. Scopolamine group ($P<0.001$), TRM group vs. Sco. +HEO3% group ($P < 0.01$), Scopolamine group vs. Sco. +HEO1% group ($P<0.001$), for the swimming time (Fig. 13 a.).

In additionally, Tukey's post hoc analysis to detect a significant difference between control group vs. TRM group ($P<0.0001$), control group vs. Sco. +HEO1% group ($P<0.01$), TRM group vs. the Scopolamine group ($P<0.0001$), Scopolamine group vs. Sco. +HEO1% group ($P<0.0001$) and Scopolamine group vs. Sco. +HEO3% group ($P<0.001$) for the immobility time (Fig. 13 b.).



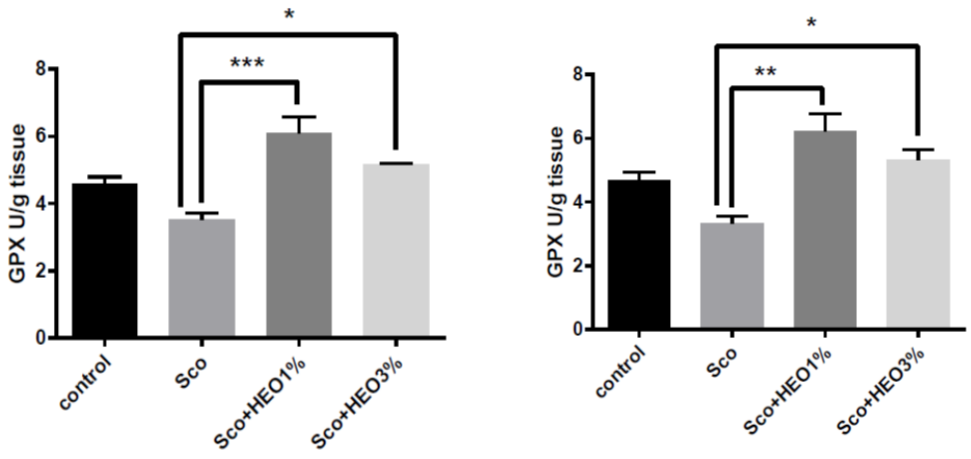
a. b.

Figure 13. Effects of the inhaled *Hypericum scabrum* essential oil (HEO1% and HEO3%) in the forced swimming test, in the scopolamine (Sco.)-treated rats, a. swimming time and b. immobility time.

3.6. Effect of the *Hypericum Scabrum* Essential Oil on GPX (Glutathione Peroxidase) Activities

For the GPX special activity assessed in the rat hippocampal homogenates, one-way ANOVA to detect a significant all over the difference between groups ($F(3,8) = 15.13$, $P<0.005$). And, Tukey's post hoc analysis exposed significant differences between the control group vs. Sco. +HEO1% group ($P<0.05$), Scopolamine group vs. Sco. +HEO1% group ($P<0.001$) and Scopolamine group vs. Sco. +HEO3% group ($P<0.05$) for GPX specific activity (Fig. 14 a.).

For GPX special activity assessed in the rat amygdala homogenates, ANOVA to detect a significant all over effect ($F(3,8) = 11.92$, $P<0.005$). And, Tukey's post hoc analysis exposed significant differences between Scopolamine group vs. Sco. +HEO1% group ($P<0.005$) and Scopolamine group vs. Sco. +HEO3% group ($P<0.05$) for GPX-special activity (Fig. 14 b.).



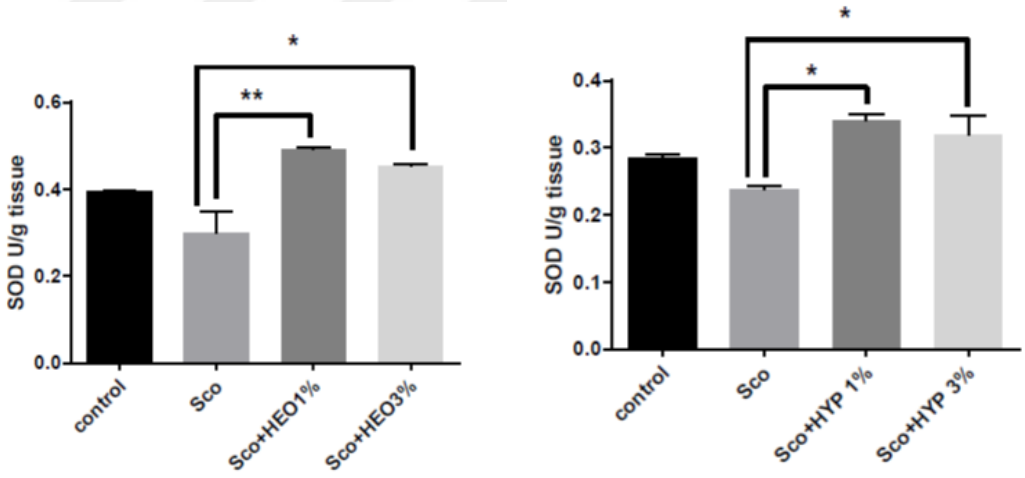
a. Hippocampus b. Amygdala

Figure 14. Effect of inhalation *Hypericum scabrum* essential oil (HEO1% and HEO3%) on GPX specific activities in the scopolamine (Sco.)-treated rats, a. Hippocampus, b. Amygdala

3.7. Effect of the *Hypericum Scabrum* Essential Oil on SOD (Superoxide Dismutase) Activities

For the SOD special activity assessed in the rat hippocampal homogenates, one-way ANOVA to detect a significant all over the difference between groups ($F(3,8) = 10.88$, $P<0.005$). And, Tukey's post hoc analysis exposed significant differences between Scopolamine group vs. Sco. +HEO1% group ($P<0.005$) and Scopolamine group vs. Sco. +HEO3% group ($P<0.05$) for SOD special activity (Fig. 15 a.).

For SOD special activity assessed in the rat amygdala homogenates, ANOVA to detect a significant all over effect ($F(3,8) = 7.249$, $P<0.05$). And, Tukey's post hoc analysis exposed significant differences between Scopolamine group vs. Sco. +HEO1% group ($P<0.05$) and Scopolamine group vs. Sco. +HEO3% group ($P<0.05$) for SOD-special activity (Fig. 15 b.).



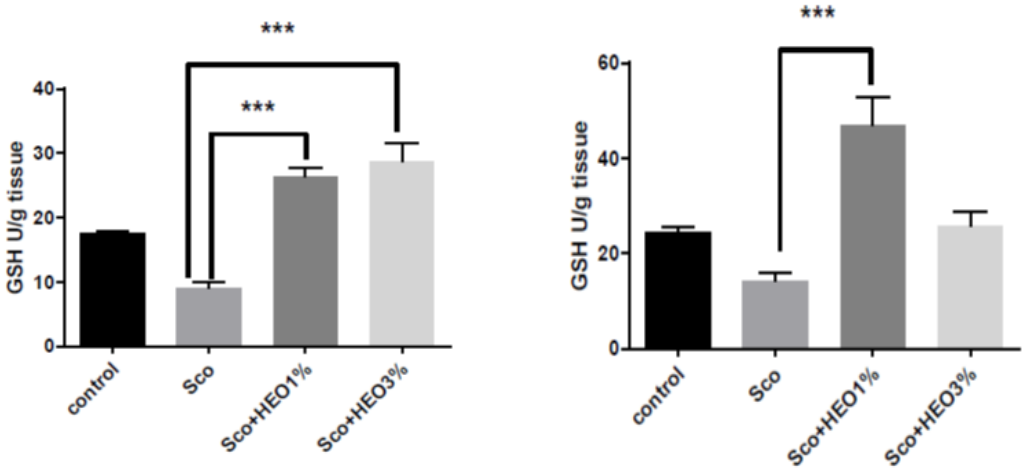
a. Hippocampus b. Amygdala

Figure 15. Effects of inhaled *Hypericum scabrum* essential oil (HEO1% and HEO3%) on SOD specific activities in the scopolamine (Sco.)-treated rats, a. Hippocampus, b. Amygdala.

3.8. Effect of the *Hypericum Scabrum* Essential Oil on Total Content of Reduced GSH (Glutathione) Levels

For the all volumes of decrease GSH assessed in the rat hippocampal homogenates, one-way ANOVA to detect a significant all over the difference between groups ($F(3,8) = 28$, $P<0.0001$). And, Tukey's post hoc analysis exposed significant differences between the control group vs. Scopolamine group ($P<0.05$), control group vs. Sco. +HEO1% group ($P<0.05$), control group vs. Sco. +HEO3% group ($P<0.01$), Scopolamine group vs. Sco. +HEO1% group ($P<0.0005$) and Scopolamine group vs. Sco. +HEO3% group ($P<0.0005$) for the all volumes of decrease GSH (Fig. 16 a.).

For the all volumes of decrease GSH assessed in the rat amygdala homogenates, ANOVA to detect a significant all over effect ($F(3,8) = 14.93$, $P<0.005$). And, Tukey's post hoc analysis exposed significant differences between the control group vs. Sco. +HEO1% group ($P<0.01$) and Scopolamine group vs. Sco. +HEO1% group ($P<0.001$), Sco. +HEO1% group vs. Sco. +HEO3% group ($P<0.05$) for the all volumes of decrease GSH (Fig. 16 b.).



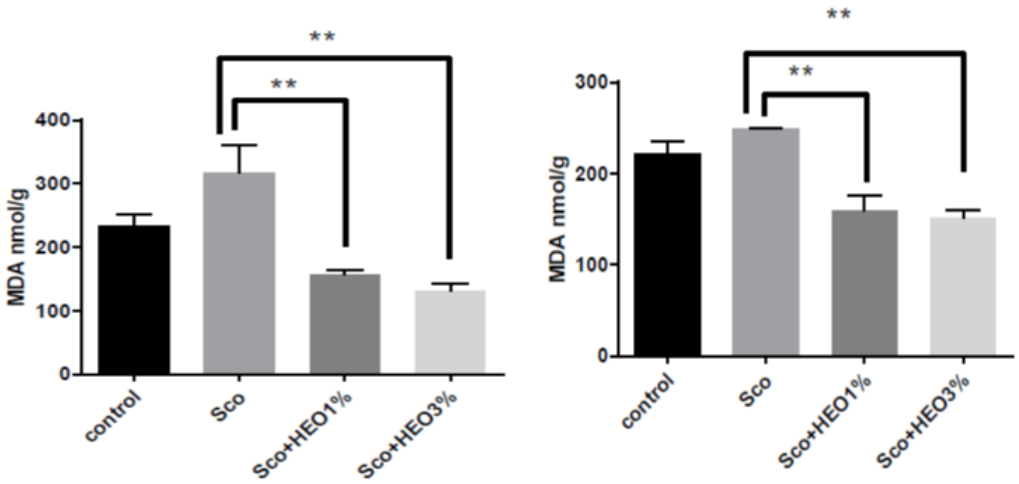
a. Hippocampus b. Amygdala

Figure 16. Effects of inhaled *Hypericum scabrum* essential oil (HEO1% and HEO3%) on reducing GSH levels in the scopolamine (Sco.)-treated rats, a. Hippocampus, b. Amygdala.

3.9. Effect of the *Hypericum Scabrum* Essential Oil on Total Content of Reduced MDA (Malondialdehyde) Levels

For the MDA level assessed in the rat hippocampal homogenates, one-way ANOVA to detect a significant all over the difference between groups (F (3,8) =11. 3, P<0.005). And, Tukey's post hoc analysis exposed significant differences between Scopolamine group vs. Sco. +HEO1% group (P<0.01) and Scopolamine group vs. Sco. +HEO3% group (P<0.005) for MDA level (Fig. 17 a.).

For the MDA levels assessed in the rat amygdala homogenates, ANOVA to detect a significant all over effect (F (3,8) =15. 64, P<0.001). And, Tukey's post hoc analysis exposed significant differences between the control group vs. Sco. +HEO1% group (P<0.05), control group vs. Sco. +HEO3% group (P<0.05), Scopolamine group vs. Sco. +HEO1% group (P<0.005) and Scopolamine group vs. Sco. +HEO3% group (P<0.005) for MDA level (Fig. 17 b.).



a. Hippocampus b. Amygdala

Figure 17. Effects of inhaled *Hypericum scabrum* essential oil (HEO1% and HEO3%) on MDA levels in the scopolamine (Sco.)-treated rats, a. Hippocampus, b. Amygdala

These obtained results protection the hypothesis that the *H. scabrum* extracted essential oil may have caused to reduce neuronal oxidative stress.

4. DISCUSSION AND CONCLUSION

4.1. Discussion

One of the old treatment is the use of aromatic herbs to alleviation numerous diseases. In actual fact, aromatic herbs have been used for thousands of years by different folks in all countries in the world, like Turkey and Iraq. Pharmacological searches supply scientific assists in the traditional and conventional utilize of aromatic medical herbs and aromatherapy; however, most clinical experiments are needful concerning to their power to be effective in arranging to set up a direction for their use in ordinary health care (Linck et al., 2009).

The extracted essential oil of *H. scabrum* which analyzed by the GC-MS/FID is monoterpene hydrocarbons and contain α-pinene (51.3 %), β-pinene (7.7 %), and Spathulenol (3.4 %), which measured for 62.4% of the total *H. scabrum* essential oil, as the important constituents of the extracted essential oil, proposal that these components could be liable for the watched anxiolytic antidepressant- like behaviour in scopolamine-treated rats. From these monoterpenes, α-pinene (51.3%) was recognized in big numbers and it has been published to exhibit anxiolytic results (Satou et al., 2014; Kasuya et al., 2013). The monoterpene β-pinene (7.7%) recognized in *H. scabrum* essential oil as the chief and important active chemical part exhibited antidepressant-like and sedative-like action and result was published (Guzmán-Gutiérrez et al., 2012).

The chief aim and goal of the present research is to estimate the spatial memory exhibition of the rats inhaled or took extracted essential oil of *Hypericum scabrum* and disposed to scopolamine. For this aim, we utilized two well-characterized hippocampus-dependent spatial memory tasks: Y-maze, radial arm-maze. These behavioural works able to experiments hippocampus-dependent short-term, long-term and spatial memory essaying that are especially changed by Alzheimer's D (Park et al., 2012). Also, 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). This obtains clearly showed that take and inhalation of the *H. scabrum* extracted essential oil

keep and support spatial memory development in a rat model of scopolamine-induced acquisition and memory damage.

The both doses (especially in low dose) of *H. scabrum* extracted essential oil in scopolamine- treated rats significantly to make bettered spatial working memory in the Y-maze task, as proved by the development of spontaneous alternation percentage as versus with scopolamine alone-treated rats. Our conclusion proposals that the both doses of *H. scabrum* essential oil (1 and 3 %) utilized in our research exhibits to make bettered result in learning and profit of the short-term memory of scopolamine-treated rats in the Y-maze task. Though, no significant differences were watched between 1% and 3% dose of *H. scabrum* essential oil on spatial working memory in the Y-maze task.

Scopolamine-treated rats inhaled *H. scabrum* extracted essential oil showed a recovery and progress of working memory in the radial arm-maze task as versus with scopolamine alone-treated rats. 1% and 3% doses of took *H. scabrum* essential oil non-significantly developed long-term memory of scopolamine-treated rats, discovered by reference memory in the radial arm-maze task. These results to point that inhalation of the *H. scabrum* essential oil acts like an important function in spatial memory forming. In other side, 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., 2014).

Our research was also aimed to test anxiety and depressive-like response after the inspiration of the *Hypericum. scabrum* essential oil (1% and 3 %, in 21 non-stop days) in rats objected or case to take of scopolamine via injection. Therefore, take on scopolamine reasons an anxiety-like behavior and depressive-like response in agreement with our early and front verifications (Hughes et al., 2004; Smythe et al., 1996). In a research that measured light-dark superiority, it was spreading that scopolamine (2 mg/kg) induced the amount of passing to the light side (Hughes et al., 2004). Also, in the black-white apparatus, scopolamine (2 mg/kg) was obtained to develop anxiety-related behaviour on both activities related, also activity non-related parameters (Smythe et al., 1996).

The elevated plus-maze is diagnosed as a precious model to forebode the anxiolytic or anxiogenic-like results of medicines in animals, especially rodents (Blainski et al., 2010).

Alao, The elevated plus-maze is recognized as a valuable model able to predict anxiolytic- or anxiogenic-like effects of drugs (Aydin et al., 2015). Our data showed that injection of scopolamine significantly reduced the percentage of the amount of crossings and the number of open-arm entries in the elevated plus maze task, two demonstrator parameters of anxiety. This demonstrates that the scopolamine-treated rats experienced very amounts of anxiety and were proper for measuring the probable anxiolytic matters as *H. scabrum* essential oil (Hayashi et al., 2012). Moreover, then the scopolamine-treated rats being inhaled *H. scabrum* essential oil (HEO1% and HEO3%), the % of number of arm crossings significantly elevated in the Sco+HEO3% group as versus with scopolamine-alone treated rats. And, the amount of open arm entries elevated in the Sco.+HEO3% as versus with scopolamine-alone treated rats. Significant differences were watched between 1% and 3% of *H. scabrum* extracted essential oil (HEO1% and HEO3%) on the % of number of arm crossings and on the number of open arm entries in the elevated plus-maze test. These effects are the facts that the benzodiazepine diazepam (DZP), celebrate as positive standard anxiolytic (Mansouri et al., 2014), was utilized as a positive control relative to the *H. scabrum* essential oil (HEO1% and HEO3%) in total, this experimental situation. As anticipated, DZP made significant increased in the percentage of number of arm crossings and the number of open-arm entries as compared with scopolamine-alone treated rats. These numbers are stable with the conclusions of high amounts of anterior researches, which have evidences 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; Adebesin et al., 2015). The pharmacological action of diazepam upgrades the effect 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 plus-maze (the % of number of arm crossings and the amount of open-arm entries) exposed 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 sedative-like or downer act and work (Guzmán-Gutiérrez et al., 2012). A preceding research showed no difference between the potentiated reaction or response of GABA on GABAA receptors in the existence of α-pinene and β-pinene (Aoshima and Hamamoto, 1999), reported that both have a sedative effect. In light of these reports, this high-

α-pinene (51.3%) and β-pinene (7.7%) consisting *H. scabrum* essential oil has developed the anxiolytic-like behaviour and anti-depressive-like response in scopolamine-treated rats.

Our result shows that injection of scopolamine significantly reduced the swimming time and developed the immobility time as versus with the control group rats, two indications parameters of depression (Bonito-Oliva et al., 2014), or The forced swimming task has been validated as a suitable tool to test the antidepressant properties of medications (Cioanca et al., 2014). This marks that the scopolamine alone treated rats showed depression. Then being exhibited to 1% and 3% of *H. scabrum* essential oil (HEO1% and HEO3%), the swimming time significantly elevated, particularly in the Sco.+HEO1%. And, the reduction of the immobility time, particularly in the Sco.+HEO1% was also watched. These conclusions suggested that *H. scabrum* extracted essential oil, but particularly HEO1%, possesses a powerful antidepressant-like reaction to an irremediable stress. In the present research, tramadol (TRM), as a positive control, produced significant elevated at the swimming time and decrease in the immobility time as versus with scopolamine-alone treated rats. Tramadol is an only medicine treat with more styles of act. It is a feeble agonist of the μ-opioid receptor, but it also prevents 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).

Additionally, it is significant to attend that oxidative stress accepts 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 simple to pass redox-reaction and guidance to radicals' forming and shows comparatively weak antioxidant defends systems (Walton et al., 2012). Scopolamine is associated with elevated oxidative stress in the complete brain, also in especially organizations depended with remembering and teach (Pachauri et al., 2012).

Our research also assessed whether memory damaged contained by scopolamine is connected to changed oxidative stress indices. Scopolamine alone-treated rats had decreased SOD in hippocampal and amygdala, Scopolamine alone-treated rats had decreased both of hippocampal and amygdala in GPX, and special activities, along with reduced contain of decreased both of hippocampal and amygdala in GSH, and in MDA, levels in the hippocampal

and amygdala homogenates. The reduces of the SOD special activities visible to parallel developments in the MDA levels in the hippocampal and amygdala homogenates proposal that these incidents are a necessity to clean superoxide radicals caused by scopolamine. Protein oxidation is an important factor in olden and age-related neurodegenerative disorders (Stadtman, 1992). MDA is the great, plentiful personal aldehyde obtaining from lipid peroxidation and can be supposed an indicator of lipid peroxidation (Hritcu et al., 2014). Additionally, high amount of researches has showed the strong positive relation that memory damages in the scopolamine- induced amnesic rats report same plans of oxidative harm in the peoples with amnesic MCI (Lee et al., 2010).

The remedy of scopolamine-induces amnesic rats with the *H. scabrum* essential oil significantly decreased the MDA amount and restored the special activities of SOD and GPX, and also the whole amount of decreased GSH in the hippocampal and amygdala homogenates. This result showed that the *H. scabrum* extracted essential oil have strong antioxidant activity by scavenging reactive oxygen species (ROS) and using a preservative effect versus oxidative stress caused by scopolamine.

4.2. Conclusion

Taken together, our findings suggest that the *Hypericum scabrum (*Hypericaceae) extracted essential oil to make a better spatial memory formation and decreased anxiety and depressive like behavior according to the statistical analysis. In addition, it also showed antioxidant effects by reduction of oxidative stress resulted by scopolamine in the rat brain (hippocampal and amygdala). In conclusion, inhalation of *H. scabrum* essential oil might offer a useful and periodic or supplementary selection in either the stoppage or the remedy of a psychiatric state nearly depended on Alzheimer's D situation. Also, in some tests 1% and in some other 3% of essential oil had more activity, but we suggested to use that 1% of *H. scabrum* essential oil, because this percentage had more positive result on the rat for both behavioral and chemical tests.

REFERENCES

Adams, R.P., 2007. Identification of essential oil by Gas Chromatography/ Mass Spectroscopy. Allured Publishing Corporation, Carol Stream, Illinois.

Adebesin, I.F., Akindele, A.J., Adeyemi, O.O,. 2015. Evaluation of neuropharmacological effects of aqueous leaf extract of *Albizia glaberrima* (Leguminosae) in mice.J Ethnopharmacol, 160, 101.

Ades, T.B., 2009. "Aromatherapy". American Cancer Society Complete Guide to Complementary and Alternative Cancer Therapies (2nd ed.). American Cancer Society. pp. 57–60.

Amaducci, L.A., Rocca, W.A., Schoenberg, B.S., 1986. Origin of the Distinction between Alzheimer's Disease and Senile Dementia: How History Can Clarify Nosology. Neurology, 36(11):1497–9.

American Psychiatric Association., 2000. Diagnostic and statistical manual of mental disorders: DSM-IV-TR (4th Edition Text Revision ed.). Washington, DC: American Psychiatric Association.

Antoine, C., Antoine, P., Guermonprez, P., Frigard, B,. 2004. Awareness of Deficits and Anosognosia in Alzheimer's Disease. L'Encéphale, 30(6):570–7.

Aoshima, H., Hamamoto, K., 1999**.** Potentiation of GABAA receptors expressed in Xenopus oocytes by perfume and phytoncid. Biosci. Biotechnol. Biochem, 63, 743.

Arnáiz, E., Almkvist, O., 2003. Neuropsychological Features of Mild Cognitive Impairment and Preclinical Alzheimer's Disease. Acta Neurologica Scandinavica, 179:34–41.

Atanasov, A.G., Waltenberger, B., Pferschy-Wenzig, E.M., Linder, T., Wawrosch, C., Uhrin, P., Temml, V., Wang, L., Schwaiger, S., Heiss, E.H., Rollinger, J.M., Schuster, D., Breuss, J.M., Bochkov, V., Mihovilovic, M.D., Kopp, B., Bauer, R., Dirsch, V.M., Stuppner, H., 2015. Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnol Adv. V. 33(8): 1582-1614.

Ayan, A.K., Yanar, P., Cirak, C., & Bilgener, M., 2007. Diurnal variation of total phenols in some Hypericum species from Turkey during their phenological cycles. Bangladesh Journal of Botany, 36, 39–46.

Aydin, E., Hritcu, L., Dogan, G., et al., 2015. The effects of inhaled *Pimpinella peregrine* essential oil on scopolamine-induced memory impairment, anxiety, and depression in laboratory rats. Mol Nurobiol. 53: 6557-6567.

Bäckman, L., Jones, S., Berger, A.K., Laukka, E.J., Small, B.J., 2004. Multiple Cognitive Deficits During the Transition to Alzheimer's Disease. Journal of Internal Medicine, 256(3):195–204.

Ballard, C., Gauthier, S., Corbett, A., et al., 2011. "Alzheimer's disease." Lancet 377 (9770): 1019–31.

Berchtold, N.C., Cotman, C.W., 1998. Evolution in the Conceptualization of Dementia and Alzheimer's disease: Greco-Roman Period to the 1960s. Neurobiology of Aging. 19 (3):173–189.

Berrios, G.E., 1990. Alzheimer's Disease: A Conceptual History. Int. J. Ger. Psychiatry, 5(6):355–365.

Blacker, D., Albert, M.S., Bassett, S.S., et al., 1994. Reliability and validity of NINCDS-ADRDA criteria for Alzheimer's disease. The National Institute of Mental Health Genetics Initiative. Archives of Neurology, 51(12):1198–204.

Blainski, A., Piccolo, V.K., Mello, J.C.P., de Oliveira, R.M.W., 2010. Dual effects of crude extracts obtained from Petiveria alliacea L. (Phytolaccaceae) on experimental anxiety in mice.Ethnopharmacol J., 128, 541.

Boller, F., Forbes, M.M., 1998. History of Dementia and Dementia in History: An Overview. Journal of the Neurological Sciences, 158(2):125–33.

Bonin-Guillaume, S., Zekry, D., Giacobini, E., Gold, G., Michel J.P., 2005. Impact économique de la démence (English: The Economical Impact of Dementia). Presse Médicale, 34(1):35–41.

Bonito-Oliva, A., Masini, D., Fisone, G., 2014. A mouse model of non-motor symptoms in Parkinson's disease: focus on pharmacological interventions targeting affective dysfunctions.Front Behav. Neurosci, 8, 290.

Bouras, C., Hof, P.R., Giannakopoulos, P., Michel, J.P., Morrison, J.H., 1994. Regional Distribution of Neurofibrillary Tangles and Senile Plaques in the Cerebral Cortex of Elderly Patients: A Quantitative Evaluation of a One-year Autopsy Population from a Geriatric Hospital. Cerebral Cortex, 4(2):138–50.

Braak, H., Del, T.K., 2012. Where, when, and in what form does sporadic Alzheimer's disease begin? Current Opinion in Neurology, 25(Pt 6):708–14.

Brandner, S., 2015. "Evidence for human transmission of amyloid-β pathology and cerebral amyloid angiopathy." Nature 525 (7568): 247–50.

Bredesen, D.E., Rao R.V., Mehlen P., 2006. "Cell death in the nervous system". Nature. 443 (7113): 796–802.

Brewer, G.J., 2012. Copper excess, zinc deficiency, and cognition loss in Alzheimer's disease. BioFactors, 38(2):107–113.

Budzynska, B., Boguszewska-Czubara, A., Kruk-Slomka, M., Skalicka-Wozniak, K., Michalak, A., Musik, I., Biala, G., 2014. Effects of imperatorin on scopolamine-induced cognitive impairment and oxidative stress in mice. Psychopharmacol (Berl), 232(5):931-42.

Burns, A., Iliffe, S., 2009. "Alzheimer's disease". 5;338:b158.

Burns, A., Iliffe, S., 2009. "Dementia.". BMJ (Clinical research ed.), 338:b75.

Caraci, F., Crupi, R., Drago, F., Spina, E., 2011. Metabolic drug interactions between antidepressants and anticancer drugs: Focus on selective serotonin reuptake inhibitors and hypericum extract. Current drug metabolism 12 (6): 570–7.

Carlesimo, G.A., Oscar-Berman, M., 1992. Memory Deficits in Alzheimer's Patients: A Comprehensive Review. Neuropsychology Review, 3(2):119–69.

Carrubba, A., and Scalenghe, R., 2012. Scent of Mare Nostrum **—** Medicinal and Aromatic Plants (MAPs) in Mediterranean soils. Journal of the Science of Food and Agriculture 92 (6).

Caspani, O., Reitz, M.C., Ceci, A., Kremer, A., 2014. Tramadol reduces anxiety-related and depression-associated behaviors presumably induced by pain in the chronic constriction injury model of neuropathic pain in rats. Treede. Pharmacol. Biochem. Behav, 124, 290-6.

Cataldo, J.K., Prochaska, J.J., Glantz, S.A., 2010. Cigarette smoking is a risk factor for Alzheimer's disease: An analysis controlling for tobacco industry affiliation. Journal of Alzheimer's Disease, 19(2):465–80.

Chun, W., Johnson, G.V., 2007. The Role of Tau Phosphorylation and Cleavage in Neuronal Cell Death. Frontiers in Bioscience, 12:733–56.

Cioanca, O., Hritcu, L., Mihasan, M., Trifan, A., Hancianu, M., 2014. Inhalation of coriander volatile oil increased anxiolytic-antidepressant like behaviors and decreased oxidative status in beta-amyloid (1-42) rat model of Alzheimer's disease. Physiology and behavior, V 131, p 68-74.

Clarfield, A.M., 2003. The Decreasing Prevalence of Reversible Dementias: An Updated Meta-analysis. Archives of Internal Medicine, 163(18):2219–29.

Coles, William, 1657. Adam in Eden, or, Natures paradise. A Book. Topics, botany, medical, early works to 1800, materia medica, vegetable. Pages 638.

Cruz, V.T., Pais, J., Teixeira, A., Nunes, B., 2004. The Initial Symptoms of Alzheimer Disease: Caregiver Perception. Acta Médica Portuguesa, 17(6):435–44.

Cryan, J.F., Markou, A., Lucki, I., 2002. Assessing antidepressant activity in rodents: recent developments and future needs. Trends Pharmacol Sci 23: 238-245.

Deane, R., Zlokovic, B.V., 2007. "Role of the blood-brain barrier in the pathogenesis of Alzheimer's disease." Current Alzheimer research 4 (2): 191–7.

Dementia, 2011. Supporting people with dementia and their carers in health and social care, NICE Clinical Guideline.

"**Dementia",** 2015. MedlinePlus. U.S. National Library of Medicine.

Desikan, R.S., Cabral, H.J., Hess, C.P., et al., 2009. Automated MRI Measures Identify Individuals with Mild Cognitive Impairment and Alzheimer's Disease. Brain, 132(Pt 8):2048–57.

Dubois, B., Feldman, H.H., Jacova, C., et al., 2007. Research Criteria for the Diagnosis of Alzheimer's Disease: Revising the NINCDS-ADRDA Criteria. Lancet Neurology, 6(8):734–46.

Dumont, M., Beal, M.F., 2011. Neuroprotective strategies involving ROS in Alzheimer disease. Free Radic Biol Med 51:1014–1026.

Eastonn, A., Douchamps, V., Eacott, M., Lever, C., 2012. A specific role for septohippocampal acetylcholine in memory? Neuropsychologia 50:3156–3168.

Ebert, U., Kirch, W., 1998. Scopolamine model of dementia: electroencephalogram findings and cognitive performance. Eur J Clin Invest 28:944–949.

Edgar, J.D., Elias, B., Adnan, B., 2002. "Biotechnology and the developing world". Electronic Journal of Biotechnology 5 (1), vol5-issue1-fulltext-1.

Eikelenboom, P., van Exel, E., Hoozemans, J.J., Veerhuis, R., Rozemuller, A.J., van Gool, W.A., 2010. Neuroinflammation – An Early Event in Both the History and Pathogenesis of Alzheimer's Disease. Neuro-Degenerative Diseases, 7(1–3):38–41.

Emamghoreishi, M., Khasaki, M., Aazam, M.F., 2005. Coriandrum sativum: evaluation of its anxiolytic effect in the elevated plus-maze. JEthnopharmacol 96, 365.

Fabricant, D.S., Farnsworth, N.R., 2001. The value of plants used in traditional medicine for drug discovery. Environ. Health Perspect. 109 Suppl 1 (Suppl 1): 69–75.

Fine Gardening, 2015.

Förstl, H., Kurz, A., 1999. Clinical Features of Alzheimer's Disease. European Archives of Psychiatry and Clinical Neuroscience, 249(6):288–290.

Forbes, D., Thiessen, E.J., Blake, C.M., Forbes, S.C., Forbes, S., 2013. "Exercise programs for people with dementia". The Cochrane Database of Systematic Reviews.

Foyet, H.S., Tsala, D.E., Bouda, A.A., Hritcu, L., 2012. Anxiolytic and antidepressant-like effects of the aqueous extract of *Alafia multiflora* stem barks in rodents. Advances in Pharmacological Sciences. V 2012, p 8.

Francis, P.T., Palmer, A.M., Snape, M., Wilcock, G.K., 1999. The Cholinergic Hypothesis of Alzheimer's Disease: a Review of Progress. Journal of Neurology, Neurosurgery, and Psychiatry, 66(2):137–47.

Frank, E.M., 1994. Effect of Alzheimer's Disease on Communication Function. Journal of the South Carolina Medical Association, 90(9):417–23.

Gauthier, Serge, 2006. Clinical diagnosis and management of Alzheimer's disease (3rd Ed.). Abingdon, Oxon: Informa Healthcare. pp. 53–54.

Geldmacher, D.S., Whitehouse, P.J., 1997. Differential Diagnosis of Alzheimer's Disease. Neurology, 48(5 Suppl 6):S2–9.

Gioti, E.M., Fiamegose, Y.C., Skalkos, D.C., & Stalikas, C.D., 2009. Antioxidant activity and bioactive components of the aerial parts of Hypericum perforatum L. from Epirus, Greece. Food Chemistry, 117, 398–404.

Gold, D.P., Reis, M.F., Markiewicz, D., Andres, D., 1995. When Home Caregiving Ends: A Longitudinal Study of Outcomes for Caregivers of Relatives with Dementia. Journal of the American Geriatrics Society, 43(1):10–6.

Goldrosen, M.H., Straus, S.E., 2004. "Complementary and alternative medicine: assessing the evidence for immunological benefits" (PDF). Nature Perspectives. 4 (11): 912–921.

Gradinariu, V., Cioanca, O., Hritcu, L., Trifan, A., Gille, E., Hancianu, M,. 2014. Comparative efficacy of Ocimum sanctum L. And Ocimum basilicum L. essential oils against amyloid beta (1–42)- induced anxiety and depression in laboratory rats. 14: 567.

Grundman, M., Petersen, R.C., Ferris, S.H., et al., 2004. "Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials". Arch. Neurol. 61 (1): 59–66.

Guzmán-Gutiérrez, S.L., Gómez-Cansino, R., García-Zebadúa, J.C., Jiménez-Pérez, N.C., Reyes-Chilpa, R., 2012. Antidepressant activity of Litsea glaucescens essential oil: Identification of β-pinene and linalool as active principles. J. Ethnopharmacol, 143, 673.

Hardy, J., Allsop, D., 1991. Amyloid Deposition as the Central Event in the Aetiology of Alzheimer's Disease. Trends in Pharmacological Sciences, 12(10):383–88.

Harvey, P.D., Moriarty, P.J., Kleinman, L., et al., 2005. The Validation of a Caregiver Assessment of Dementia: the Dementia Severity Scale. Alzheimer Disease and Associated Disorders, 19(4):186–94.

Hashimoto, M., Rockenstein, E., Crews, L., Masliah, E., 2003. Role of Protein Aggregation in Mitochondrial Dysfunction and Neurodegeneration in Alzheimer's and Parkinson's Diseases. Neuromolecular Medicine, 4(1–2):21–36.

Hayashi, Y., Sogabe, S., Hattori, Y., Tanaka, J., 2012. Anxiolytic and hypnotic effects in mice of roasted coffee bean essential compounds. Neurosci Lett 531:166–169.

Hernández, F., Avila, J., 2007. Tauopathies. Cellular and Molecular Life Sciences, 64(17):2219–33.

Hines, Terence, 2003. Pseudoscience and the Paranormal (2nd ed.). Amerst, New York: Prometheue Books.

Holmes, C., Boche, D., Wilkinson, D., et al., 2008. Long-term Effects of Abeta42 Immunisation in Alzheimer's Disease: Follow-up of a Randomised, Placebo-controlled Phase I Trial. Lancet, 372(9634):216–23.

Hooper, N.M., 2005. Roles of Proteolysis and Lipid Rafts in the Processing of the Amyloid Precursor Protein and Prion Protein. Biochemical Society Transactions, 33(Pt 2):335–8.

Hritcu, L., Noumedem, J., Cioanca, O., Hancianu, M., Kuete, V., Mihasan, M., 2014. Methanolic extract of Piper nigrum fruits improves memory impairment by decreasing brain oxidative stress in amyloid beta (1–42) rat model of Alzheimer's disease. Cell Mol Neurobiol 34:437–449.

Hughes, R.N., Desmond, C.S., Fisher, L.C.E., 2004. Room novelty, sex, scopolamine and their interactions as determinants of general activity and rearing, and light-dark preferences in rats.Behav. Processes, 67, 173-81.

Iqbal, K., Alonso, A.C, Chen, S., et al., 2005. Tau Pathology in Alzheimer Disease and Other Tauopathies. Biochimica et Biophysica Acta, 1739(2–3):198–210.

Jaunmuktane, Z., Mead, S., Ellis, M., Wadsworth, J.D., Nicoll, A.J., Kenny, J., Launchbury, F., Linehan, J., Richard-Loendt, A., Walker, A.S., Rudge, P., Collinge, J., Goedert, M., Spillantini, M.G,, Crowther, R.A., 1991. Tau Proteins and Neurofibrillary Degeneration. Brain Pathology, 1(4):279–86.

Javidnia, K., Miri, R., Soltani, M., Gholami, M., & Khosravi, A.M., 2008. Essential oil composition of four Hypericum species from Iran. Chemistry of Natural Compounds, 44, 374–377.

Jelicic, M., Bonebakker, A.E., Bonke, B., 1995. Implicit Memory Performance of Patients with Alzheimer's Disease: A Brief Review. International Psychogeriatrics, 7(3):385–392.

John, T., Arnason, R.M., John, T., Romeo, 2013. Phytochemistry of Medicinal Plants. Springer Science & Business Media.

Kastenholz, B., Garfin, D.E., Horst, J., Nagel, K.A., 2009. Plant Metal Chaperones: A Novel Perspective in Dementia Therapy. Amyloid, 16(2):81–3.

Kasuya, H., Hata, E., Satou, T., Yoshikawa, M., Hayashi, S., Masuo, Y., Koike, 2013. Effect on emotional behavior and stress by inhalation of the essential oil from Chamaecyparis obtusa. Nat K. Prod. Commun, 8, 515.

Katzman, R., Terry, R.D., Bick, K.L., (editors). 1978. Alzheimer's Disease: Senile Dementia and Related Disorders. New York: Raven Press. p. 595.

Kent, H., 1997. "Ignore Growing Patient Interest in Alternative Medicine at Your Peril - MDs Warned" (PDF). Canadian Medical Association Journal. 157 (10): 1427–1428.

Kizil, G., Kizil, M., Yavuz, M., Emen, S., & Hakimog˘ lu, F., 2008. Antioxidant activities of ethanol extracts of Hypericum triquetrifolium and Hypericum scabroides. Pharmaceutical Biology, 46, 231–242.

Klafki, H.W., Staufenbiel, M., Kornhuber, J., Wiltfang, J., 2006. Therapeutic Approaches to Alzheimer's Disease. Brain, 129(Pt 11):2840–55.

Klinkenberg, I., Blokland, A., 2010. The validity of scopolamine as a pharmacological model for cognitive impairment: a review of animal behavioral studies. Neurosci Biobehav Rev 34:1307–1350.

Kotzbauer, P.T., Trojanowsk, J.Q., Lee, V.M., 2001. Lewy Body Pathology in Alzheimer's Disease. Journal of Molecular Neuroscience, 17(2):225–32.

Kraepelin, E., Diefendorf, A., Ross, 2007. (translated by). Clinical Psychiatry: A Textbook For Students And Physicians (Reprint). Kessinger Publishing. p. 568.

Kuriyama, H., Watanabe, S., Nakaya, T., Shigemori, I., Kita, M., Yoshida, N., Masaki, D., Tadai, T., Ozasa, K., Fukui, K., Imanishi, J., 2005. "Immunological and Psychological Benefits of Aromatherapy Massage". Evidence-Based Complementary and Alternative Medicine. 2 (2): 179.

Kwon, S.H., Ma, S.X., Joo, H.J., Lee, S.Y., Jang, C.G., 2013. Inhibitory effects of Eucommia ulmoides Oliv. bark on scopolamine-induced learning and memory deficits in mice. Biomol Ther 21:462–469.

Lacor, P.N., Buniel, M.C., Furlow, P.W., et al., 2007. Aß Oligomer-Induced Aberrations in Synapse Composition, Shape, and Density Provide a Molecular Basis for Loss of Connectivity in Alzheimer's Disease. The Journal of Neuroscience, 27(4):796–807.

Lai, P.K., Roy, J., 2004. Antimicrobial and chemopreventive properties of herbs and spices. Curr. Med. Chem. 11 (11): 1451–60.

Lalonde, R., Dumont, M., Staufenbiel, M., Sturchler-Pierrat, C., Strazielle, C., 2002. Spatial Learning, Exploration, Anxiety, and Motor Coordination in Female APP23 Transgenic Mice with the Swedish Mutation. Brain Research, 956(1):36–44.

Landes, A.M., Sperry, S.D., Strauss, M.E., Geldmacher, D.S., 2001. Apathy in Alzheimer's Disease. Journal of the American Geriatrics Society, 49(12):1700–7.

Laurén, J., Gimbel, D.A., Nygaard, H.B., Gilbert, J.W., Strittmatter, S.M., 2009. Cellular Prion Protein Mediates Impairment of Synaptic Plasticity by Amyloid-β Oligomers. Nature, 457(7233):1128–32.

Lee, M.R., Yun, B.S., Park, S.Y., Ly, S.Y., Kim, S.N., Han, B.H., Sung, C.K., 2010. Anti-amnesic effect of Chong–Myung–Tang on Scopolamine-induced memory impairments in mice. J Ethnopharmacol 132:70–74.

Lidsky, T.I., 2014. "Is the Aluminum Hypothesis dead?" Journal of Occupational and Environmental Medicine 56 (5 Suppl): S73–9.

Linck, V.d.M., da Silva, A.L., Figueiró, M., Luis, P.Â., Paula, H.A., Dupont, B.F., Bastos, C.E., Sávio, N.D., Moreno, P.R.H., Elisabetsky, E., 2009. Inhaled linalool-induced sedation in mice. Phytomedicine, 303-307.

Lott, I.T., Head, E., 2005. Alzheimer Disease and Down Syndrome: Factors in Pathogenesis. Neurobiology of Aging, 26(3):383–89.

Lozano, R., Naghavi, M., Foreman, K., 2012. "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". Lancet 380 (9859): 2095–128.

Luque-Contreras, D., Carvajal, K., Toral-Rios, D., Franco-Bocanegra, D., Campos-Pena, V., 2014. Oxidative stress and metabolic syndrome: cause or consequence of Alzheimer’s disease? Oxid Med Cell Longev.

Mansouri, M.T., Soltani, M., Naghizadeh, B., Farbood, Y., Mashak, A., Sarkaki, A., 2014. A possible mechanism for the anxiolytic-like effect of gallic acid in the rat elevated plus maze.Pharmacol. Biochem. Behav, 117, 40.

Marco, L.G., Alfio, T.S., Castorina, A., Platania, C.B.M., Impellizzeri, A.A.R., Fidilio, A., Caraci, F., Bucolo, C., Drago, F., Salomone, S., 2014. Dopamine D3 receptor-dependent changes in alpha6 GABAA subunit expression in striatum modulate anxiety-like behaviour: responsiveness and tolerance to diazepam. Eur. Neuropsychopharmacol. 25 (6), 10.1016.

Martorana, A., Esposito, Z., Koch, G., 2010. "Beyond the cholinergic hypothesis: do current drugs work in Alzheimer's disease?". CNS neuroscience & therapeutics 16 (4): 235–245.

Mathew, M., Subramanian, S., 2014. In vitro screening for anticholinesterase and antioxidant activity of methanolic extracts of ayurvedic medicinal plantsused for cognitive disorders. PLoS ONE 9.

Maurer, U., Maurer, K., 2003. Alzheimer: The Life of a Physician and the Career of a Disease. New York: Columbia University Press. p. 270.

McKhann, G., Drachman, D., Folstein, M., et al., 1984. Clinical Diagnosis of Alzheimer's Disease: Report of the NINCDS-ADRDA Work Group under the Auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology, 34(7):939–44.

Medicine., 2014. Oxford Dictionaries Online. Oxford University Press.

Meek, P.D., McKeithan, K., Schumock, G.T., 1998. Economic Considerations in Alzheimer's Disease. Pharmacotherapy. 18(2 Pt 2):68–73; discussion 79–82.

Mendez, M.F., 2006. The Accurate Diagnosis of Early-onset Dementia. International Journal of Psychiatry in Medicine, 36(4):401–412.

Mendez, M.F., 2012. "Early-onset Alzheimer's disease: nonamnestic subtypes and type 2 AD". Archives of Medical Research 43 (8): 677–85.

Meskin, M.S., 2002. Phytochemicals in Nutrition and Health. CRC Press. p. 123.

Moan, R., 2009. MRI Software Accurately IDs Preclinical Alzheimer's Disease. Diagnostic Imaging.

Moreira, P.I., Nunomura, A., Nakamura, M., Takeda, A., Shenk, J.C., Aliev, G., Smith, M.A., Perry, G., 2008. Nucleic acid oxidation in Alzheimer disease. Free Radic Biol Med 44:1493–1505.

Moulay, A.J., 2010. Alternative and Complementary Therapies for Cancer: Integrative Approaches and Discovery of Conventional Drugs. Springer Science & Business Media. pp. 558.

Moulton, P.V., Yang, W., 2012. Air Pollution, Oxidative Stress, and Alzheimer's Disease. Journal of Environmental and Public Health.

Mudher, A., Lovestone, S., 2002. Alzheimer's disease-do tauists and baptists finally shake hands?. Trends in Neurosciences, 25(1):22–26.

Murray, E.D., Buttner, N., Price, B.H., 2012. "Depression and Psychosis in Neurological Practice". In Bradley WG, Daroff RB, Fenichel GM, Jankovic J. Bradley's neurology in clinical practice. (6th ed.). Philadelphia, PA: Elsevier/Saunders.

Nistor, M., Don, M., Parekh, M., et al., 2007. Alpha- and Beta-secretase Activity as a Function of Age and Beta-amyloid in Down Syndrome and Normal Brain. Neurobiology of Aging, 28(10):1493–1506.

Nygård, L., 2003. Instrumental Activities of Daily Living: A Stepping-stone Towards Alzheimer's Disease Diagnosis in Subjects with Mild Cognitive Impairment? Acta Neurologica Scandinavica, Suppl(179):42–6.

Ohkawa, H., Ohishi, N., Yagi, K., 1979. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem 95:351–358.

Ohnishi, S., Takano, K., 2004. Amyloid Fibrils from the Viewpoint of Protein Folding. Cellular and Molecular Life Sciences, 61(5):511–24.

Pachauri, S.D., Tota, S., Khandelwal, K., Verma, P.R.P., Nath, C., Hanif, K., Shukla, R., Saxena, J.K., Dwivedi, A.K., 2012. Protective effect of fruits of Morinda citrifolia L. on scopolamine induced memory impairment in mice: a behavioral, biochemical and cerebral blood flow study. Ethnopharmacol J., 139, 34-41.

Park, S.J., Jung, J.M., Lee, H.E., Lee, Y.W., Kim, D.H., Kim, J.M., Hong, J.G., Lee, C.H., Jung, I.H., Cho, Y.B., Jang, D.S., Ryu, J.H., 2012. The memory ameliorating effects of INM-176, an ethanolic extract of Angelica gigas, against scopolamine- or Ab1–42-induced cognitive dysfunction in mice. J Ethnopharmacol 143:611–620.

Pasquier, F., 1999. Early diagnosis of dementia: neuropsychology. Journal of Neurology, 246(1):6–15.

Pohanka, M., 2013. Alzheimer´s Disease and Oxidative Stress: A Review. Current Medicinal Chemistry, 21(3):356–64.

Polvikoski, T., Sulkava, R., Haltia, M., et al., 1995. Apolipoprotein E, Dementia, and Cortical Deposition of Beta-amyloid Protein. The New England Journal of Medicine, 333(19):1242–47.

Potter, G.G., Steffens, D.C., 2007. Contribution of Depression to Cognitive Impairment and Dementia in Older adults. The Neurologist, 13(3):105–17.

Priller, C., Bauer, T., Mitteregger, G., Krebs, B., Kretzschmar, H.A., Herms, J., 2006. Synapse Formation and Function is Modulated by the Amyloid Precursor Protein. The Journal of Neuroscience, 26(27):7212–21.

Querfurth, H.W., LaFerla, F.M., 2010. "Alzheimer's disease". The New England Journal of Medicine 362 (4): 329–44.

Reitz, Christiane, Mayeux, Richard., 2014. "Alzheimer disease: Epidemiology, Diagnostic Criteria, Risk Factors and Biomarkers". Biochemical pharmacology 88 (4): 640–651.

Riss, J., Cloyd, J., Gates, J., Collins, S., 2008. Benzodiazepines in epilepsy: pharmacology and pharmacokinetics.Acta Neurol. Scand, 118, 69.

Rodgers, R.J., Dalvi, A., 1997. Anxiety, defence and the elevated plus-maze. Neurosci Biobehav Rev.; 21 (6):801-10.

Samadi, S., Khadivzadeh, T., Emami, A., Moosavi, N.S., Tafaghodi, M., Behnam, H.R., 2010. The effect of Hypericum perforatum on the wound healing and scar of cesarean. Journal of alternative and complementary medicine 16 (1): 113–7.

Santibáñez, M., Bolumar, F., García, A.M., 2007. Occupational Risk Factors in Alzheimer's Disease: A Review Assessing the Quality of Published Epidemiological Studies. Occupational and Environmental Medicine, 64(11):723–732.

Satou, T., Kasuya, H., Maeda, K., Koike, K., 2014. Daily inhalation of α-pinene in mice: effects on behavior and organ accumulation. Phytother. Res, 28, 1284-7.

Schroeter, M.L., Stein, T., Maslowski, N., Neumann, J., 2009. Neural Correlates of Alzheimer's Disease and Mild Cognitive Impairment: A Systematic and Quantitative Meta-Analysis involving 1,351 Patients. NeuroImage, 47(4):1196–1206.

Shen, Z.X., 2004. Brain Cholinesterases: II. The Molecular and Cellular Basis of Alzheimer's Disease. Medical Hypotheses, 63(2):308–21.

Smythe, J.W., Murphy, D., Bhatnagar, S., Timothy, C., Costall, B., 1996. Muscarinic antagonists are anxiogenic in rats tested in the black-white box. Pharmacol. Biochem. Behav, 54, 57-63.

Solomon, A.E., Budson, P.R., 2011. Memory loss: a practical guide for clinicians.

Springbob, K., & Kutchan, Toni, M., 2009. Introduction to the different classes of natural products. In Lanzotti, Virginia. Plant-Derived Natural Products: Synthesis, Function, and Application. Springer. p. 3.

Stadtman, E., 1992. Protein oxidation and aging. Science 257:1220–1224.

Stepp, J.R., 2004. The role of weeds as sources of pharmaceuticals. Journal of Ethnopharmacology 92 (2–3): 163–166.

Su, B., Wang, X., Nunomura, A., et al., 2008. Oxidative Stress Signaling in Alzheimer's Disease. Current Alzheimer Research, 5(6):525–32.

Sun, X., Steffens, D.C., Au, R., et al., 2008. Amyloid-Associated Depression: A Prodromal Depression of Alzheimer Disease? Archives of General Psychiatry, 65(5):542–550.

Swain, Tony, ed., 1968. Plants in the Development of Modern Medicine. Harvard University Press.

Taler, V., Phillips, N.A., 2008. Language Performance in Alzheimer's Disease and Mild Cognitive Impairment: a comparative review. Journal of Clinical and Experimental Neuropsychology, 30(5):501–56.

Tiraboschi, P., Hansen, L.A., Thal, L.J., Corey-Bloom, J., 2004. The Importance of Neuritic Plaques and Tangles to the Development and Evolution of AD. Neurology, 62(11):1984–9.

Todd, S., Barr, S., Roberts, M., Passmore, A.P., 2013. "Survival in dementia and predictors of mortality: a review". International Journal of Geriatric Psychiatry 28 (11): 1109–24.

Tombaugh, T.N., McIntyre, N.J., 1992. The mini-mental state examination: a comprehensive review. Journal of the American Geriatrics Society, 40(9):922–35.

Turner, P.R., O'Connor, K., Tate, W.P., Abraham, W.C., 2003. Roles of Amyloid Precursor Protein and its Fragments in Regulating Neural Activity, Plasticity and Memory. Progress in Neurobiology, 70(1):1–32.

URL-1,http://www.mayoclinic.org/diseases-conditions/alzheimers-disease/basics/complications/con-20023871. 2014. Alzheimer’s disease complications. The Mayo Clinic.

URL-2, http://hypericum.myspecies.info/ *Hypericum* Online.

USDA (United States Department of Agriculture).gov, 2015.

Volicer, L., Harper, D.G., Manning, B.C., Goldstein, R., Satlin, A., 2001. Sundowning and Circadian Rhythms in Alzheimer's Disease. The American Journal of Psychiatry, 158(5):704–11.

Waldemar, G., Dubois, B., Emre, M., et al., 2007. Recommendations for the Diagnosis and Management of Alzheimer's Disease and Other Disorders Associated with Dementia: EFNS Guideline. European Journal of Neurology, 14(1):e1–26.

Walton, N.M., Shin, R., Tajinda, K., Heusner, C.L., Kogan, J.H., Miyake, S., Chen, Q., Tamura, K., Matsumoto, M., 2012. Adult neurogenesis transiently generates oxidative stress. PLoS One, 7 (4).

Wenk, G.L., 2003. Neuropathologic Changes in Alzheimer's Disease. The Journal of Clinical Psychiatry, 64 Suppl 9:7–10.

Xiaorui, Z., 2013. "Traditional Medicines: Definitions". WHO website. Medicines. World Health Organization.

Xu, H., Finkelstein, D.I., Adlard, P.A., 2014. Interactions of metals and Apolipoprotein E in Alzheimer's disease. Frontiers Aging Neuroscience.

Xu, P.x., Wang, S.W., Yu, X.l., Su, Y.j., Wang, T., Zhou, W.w., Zhang, H., Wang, Y.j., Liu, R.t., 2014. Rutin improves spatial memory in Alzheimer's disease transgenic mice by reducing Ab oligomer level and attenuating oxidative stress and neuroinflammation. Behav Brain Res 264:173–180.

Yegambaram, M., Manivannan, B., Beach, T.G., Halden, R.U., 2015. "Role of environmental contaminants in the etiology of Alzheimer's disease: a review." Current Alzheimer research 12 (2): 116–46.

Zainal Abidin Bin, A., Zamri, B.Y., Ahmad, F.B.A., Muhamad, A.F.B.M.N.R., Muhammad, S.H.B.M.Z., Mohd, H.B.R., Mohammad, Z.I.B.M.Z., 2015. HYDRO-DISTILLATION PROCESS IN EXTRACTING OF AGARWOOD ESSENTIAL OIL. P 203.

Zuhal, T., 2009. Variation of total hypericin, phenolic and flavonoid compounds in Hypericum triquetrifolium during its phenological cycle. Pharmaceutical Biology, 47, 285–288.

Curriculum Vitae (CV)

My name is Tariq Hassan MOHAMMED SUR, also my date and location of birth is 15/11/1981 in Iraq- Al Sulaymaneyah. We are eight persons in the family, two sisters, four brothers and parents. I was married from seven years ago. I have a son with six years old. I was graduated from Salahaddin University College of Science Department of Biology and I took Bachelor of Science (2003-2007). Additionally, I started to work in laboratory of hospital part of hematology (2008-2011) and blood bank (2011-2015). And finally, in 27/02/2015 I started to study master degree in Firat University, Graduate School of Natural and Applied Sciences, Department of Biology.