People's Democratic Republic of Algeria Ministry of Higher Education and Scientific Research

University of Larbi Tebessi-Tebessa

Faculty of Exact Sciences and Natural and Life Sciences

Department: Applied Biology

MEMORY

Presented with a view to obtaining the Master's degree

Domain: Natural and life Sciences

Spinneret: Biological Sciences

Option: Toxicology

HOW TO USE HERBAL MEDICINE TO DEAL WITH A NERVOUS BREAKDOWN

Presented by:

Mr. HAMLA Yahia **Mr. RAIS Mohamed Ilyes**

Mr. KHELAIFIA Akram

In front of the jury:

Dr. BOUCHIHA Hanene	**MCA**	**University of Tebessa**	**President**
Dr. BILAL Warda	**MAA**	**University of Tebessa**	**Examiner**
Pr. ROUABHI Rachid	**Pr**	**University of Tebessa**	**Promoter**
Dr. Sarra Zouaoui	**Dr**	**University of Tebessa**	**co-promoter**

Note: **Graduation date: 15/06/2022** ***Mention***

ملخص :

منذ العصور القديمة، كان العلاج بالنباتات من أكثر العلاجات شيوعًا وفائدة للإنسان حيث تطورت طرق العلاج بالنباتات الطبية من الحضارات القديمة حتى العصر الحديث بالتوازي مع تطور التقنيات للاستفادة من المكونات الأساسية للنباتات الطبية، وخاصة القلويدات، الفلافونويد والفينولات، وصولا إلى ظهور العلاج بالروائح من خلال الزيوت الأساسية للنباتات الطبية.

أجرينا هذه الدراسة لتقييم قدرة وتأثير العالج بالنباتات على الانهيار العصبي وأعراضه إضافة الى الامراض التنكسية، لتحديد الارتباط بينها.

لدراسة دور الأعشاب الطبية في مواجهة الانهيارات العصبية والأمراض المصاحبة لها، قمنا بإجراء العديد من الأبحاث، بدءاً بعموميات حول طب الأعشاب وأنواعها والمواد الفعالة للنباتات الطبية، بالإضافة إلى العالج بالروائح وطرق استخلاص الزيوت العطرية وأهميتها في الحد من الأمراض العصبية وآثارها.

في الفصل الثاني تدور دراستنا حول بنية الجهاز العصبي المركزي، وتأثير الانهيار العصبي عليه، وتحديد فاعلية الأعشاب الطبية في الحد من هذا المرض وآثاره، بالإضافة إلى آلية عمل مضادات الاكتئاب وآثارها السلبية وتقديم مفهوم حول الاجهاد التأكسدي واسبابه.

عرضنا في الفصل الأخير مرضين عصبيين مصاحبين للانهيار العصبي وهما القلق والزهايمر وآلية تأثير بعض النباتات الطبية مثل البابونج والخزامى في الوقاية والعلاج من هذه الأمراض.

في النهاية تم تحديد العلاقة بين استخدام الأدوية العشبية والانهيار العصبي، حيث يمكن علاج أعراض الانهيار العصبي بالنباتات الطبية وقد ثبت ذلك من خلال العديد من التجارب العلمية، ومن بين الأمراض التي يمكن أن تساعد النباتات الطبية في علاجها: الاكتئاب والقلق والعصبية والامراض التنكسية وهذا يعود لخصائص العديد من النباتات الطبية، بما في ذلك المهدئات والمنشطات والمثبطات وغيرها التي تستهدف النواقل العصبية.

كلمات مفتاحية: العلاج بالنباتات، الانهيار العصبي، العلاج بالروائح، الزيوت الأساسية، النباتات الطبية، الجهاز العصبي، مضادات الاكتئاب، القلق، الزهايمر، الأمراض التنكسية.

Résumé :

Depuis l'Antiquité, la phytothérapie est l'un des traitements les plus courants et les plus bénéfiques pour l'homme où les méthodes de traitement des plantes médicinales se sont développées depuis les civilisations anciennes jusqu'à l'ère moderne en parallèle avec le développement des techniques pour profiter des composants de base des plantes médicinales, notamment les alcaloïdes, les flavonoïdes et les phénols, jusqu'à l'émergence de l'aromathérapie à travers les huiles essentielles de plantes médicinales.

Nous avons mené cette étude pour évaluer la capacité et l'effet de la phytothérapie sur la dépression nerveuse et ses symptômes, afin de déterminer le lien entre eux.

Pour étudier le rôle des herbes médicinales contre les dépressions nerveuses et les maladies qui y sont associées, nous avons mené diverses recherches, en commençant par des généralités sur la phytothérapie, ses types et les substances actives des plantes médicinales, en plus de l'aromathérapie, des méthodes d'extraction des huiles essentielles et leur importance dans la réduction des maladies nerveuses et leurs effets.

Dans le second chapitre, notre étude tourne autour la structure du système nerveux central, de l'effet de la dépression nerveuse sur celui-ci, et de la détermination de l'efficacité des herbes médicinales pour réduire cette maladie et ses effets, en plus du mécanisme d'action des antidépresseurs et leurs effets négatifs.

Dans le dernier chapitre, nous avons présenté deux maladies neurologiques associées à la dépression nerveuse, à savoir l'anxiété et la maladie d'Alzheimer, et le mécanisme de l'effet de certaines plantes médicinales comme la camomille et la lavande dans la prévention et le traitement de ces maladies.

En fin de compte, la relation entre l'utilisation de la phytothérapie et la dépression nerveuse a été déterminée, où les symptômes de la dépression nerveuse peuvent être traités avec des plantes médicinales et cela a été prouvé par de nombreuses expériences scientifiques, et parmi les symptômes que les plantes médicinales peuvent aider à traiter sont la dépression, l'anxiété et la nervosité et cela est dû aux propriétés de nombreuses plantes médicinales, notamment les sédatifs, les stimulants, les dépresseurs, et autres...

Mots clés : phytothérapie, dépression nerveuse, aromathérapie, huiles essentielles, plantes médicinales, système nerveux, antidépresseurs, anxiété, Alzheimer.

Abstract:

Since ancient times, phytotherapy has been one of the most common and beneficial treatments for humans as the methods of treating medicinal plants developed from ancient civilizations until modern times in parallel with the development of techniques to benefit from the basic components of medicinal plants, especially alkaloids, flavonoids and phenols, leading to the emergence of aromatherapy through the essential oils of medicinal plants.

We conducted this study to evaluate the ability and effect of phytotherapy on nervous breakdown and its symptoms, to determine the link between them.

To study the role of medicinal herbs against nervous breakdowns and the diseases associated with it, we conducted various researches, starting with generalities about phytotherapy, its types and the active substances of medicinal plants, in addition to aromatherapy, methods of extracting essential oils and their importance in reducing nervous diseases and their effects.

In the second chapter, our study revolves around the structure of the central nervous system, the effect of nervous breakdown on it, and determining the effectiveness of medicinal herbs in reducing this disease and its effects, in addition to the mechanism of action of antidepressants and their negative effects.

In the last chapter, we presented two neurological diseases associated with nervous breakdown, namely anxiety and Alzheimer's, and the mechanism of the effect of some medicinal plants such as chamomile and lavender in the prevention and treatment of these diseases.

In the end, the relationship between the use of phytotherapy and nervous breakdown was determined, where the symptoms of nervous breakdown can be treated with medicinal plants and this has been proven through many scientific experiments, and among the symptoms that medicinal plants can help in treating are depression, anxiety and nervousness and this is due to the properties of Many medicinal plants, including sedatives, stimulants, depressants, and others...

Key words: phytotherapy, nervous breakdown, aromatherapy, essential oils, medicinal plants, nervous system, antidepressants, anxiety, Alzheimer.

Thanks

First of all, we would like to thank God Almighty for granting us patience and success in completing the graduation thesis. We want to express our full gratitude to ***Professor ROUABHI Rachid*** *in addition to our* ***doctor and supervisor Miss Sarra Zouaoui*** *for her humility and valuable advice in guiding, encouraging and correcting our mistakes.*

We would also like to thank all of ***Dr. BOUCHIHA Hanene*** *and* ***Dr. BILAL Warda*** *agrees to co-chair the committee to evaluate this thesis.*

We also thank all the college professors for their mastery of their work and the beautiful moments we lived together, in addition to all the people who contributed to the completion of this note.

Dedication

I dedicate this modest work to those who havedevoted their lives to my education, my dear parents, and to all my dear family members, relatives and friends, and to all the people I love and who love me.

Yahia

I dedicate this work to my dear parents, the source of my happiness, and all my family members, and to all my friends and everyone who helped me to accomplish this work.

Ilyes

I dedicate this work to my dear parents, all family, relatives and loved ones, and to every person who is dear to me and helped in this work.

Akram

List of abbreviations

ACTH… .....Adrenocorticotropic hormone.

AD .....Alzheimer’s disease

CBT… .....Cognitive behavioral therapy.

CO2… .....Carbon Dioxide.

CSF..... Cerebrospinal fluid.

CT…..... Computerized tomography

CYP2C19… .....Cytochrome P450 2C19

CYP450… .....Cytochrome P450

EHC..... Enterohepatic circulation

FDA.....Food and Drug Administration

FSH…..... Follicle-stimulating hormone.

GABAA..... γ-Aminobutyric acid type A

GAD… .....Generalized anxiety disorder

LH..... Luteinizing hormone.

MAOIs…..... Monoamine oxidase inhibitors

MRI ..... Magnetic resonance imaging

ND .....Neurodegenerative disease

NDs…..... Neurodegenerative diseases

NMDA…..... N-methyl-D-aspartate

OCD… .....Obsessive compulsive disorder

PAL .....Phenylalanine ammonia-lyase.

PNC… .....Peripheral nervous system

PTSD… .....Post-traumatic stress disorder

PVN.....Paraventricular nucleus.

SAD… ..... Social Anxiety Disorder

SCN .....Suprachiasmatic nucleus.

SFE… .....Supercritical fluid extraction

SNC… .....Central nervous system

SSRIS .....Selective serotonin reuptake inhibitor

T3… .....Triiodothyronine.

T4… .....Thyroxine.

TCAs… .....Tricyclic antidepressants

TSH .....Thyroid stimulating hormone.

UV .....Ultraviolet.

List of Figures

List of Tables

Table of Contents

General Introduction

Introduction

Neurodegenerative disease (ND) is a superordinate phrase describing various conditions that affect nerve cells and the nervous system. They are complex, fatal, disabling sicknesses that result in gradual neuronal loss in both the central nervous system (CNS) and peripheral nervous system by destruction of neuronal networks. Many of these diseases are genetic with a few caused by medical conditions like stroke while others are due to toxins or chemicals in the environment. NDs can cause problems related to movement (ataxias) or mental functioning (dementia) and can lead to death, having profound social and economic implications **(Wynford-Thomas & Robertson, 2017).**

Neurodegenerative diseases (NDs) include a number of chronic progressive disorders of the central nervous system that are caused by the degradation and subsequent loss of neurons. NDs represent one of the most important public health problems and concerns, as they are a growing cause of mortality and morbidity worldwide, particularly in the elderly. The aging of the population has contributed to the increase of NDs **(Heemels, M.T,2016) (GBD, 2017)**

Traditionally, classifications of NDs included Parkinson's disease, which is well characterized by a loss of dopaminergic nigrostriatal neurons; Huntington's disease, in which the loss of spiny, medium-sized striatal neurons occurs; and Alzheimer's disease (AD), due to diffuse cerebral atrophy. Other disorders such as primary dystonia or essential tremor were also referred to as NDs **(Burgunder, J.M,2003)**

Neurodegenerative diseases are a significant problem. According to a consensus that was developed using the Delphi method, the prevalence of Alzheimer's disease is on the rise, and an estimated 26.6 million patients with AD are reported worldwide. Furthermore, this number is estimated to increase to 106.2 million by 2050 **(Brookmeyer *et al*,2007)**

The Mental Health Foundation statistics also say that every person out of 26 in the world is exposed to a nervous breakdown due to the pressures of life and daily problems **(Gantt WH, 2006).**

It has long been known that oxidative stress may be important in the etiology of a variety of late neurodegenerative diseases. Oxidative stress has been defined as a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses, which may lead to tissue injury **(Halliwell B,1994)**

The main aim of neuroprotection is to prevent neuronal loss, prompt neuronal network regeneration, and alleviate brain dysfunction. Phytochemicals are complex compounds with multiple-target efficacy found mainly in plants **(Harvey & Cree, 2010).** Phytochemicals have disease-modifying ability by acting as antioxidants (resveratrol, hesperidin), anti-inflammatory agents (cineole, thymoquinine), inhibitors of GABAA receptors (diterpenes and cyclodepsipeptides), inhibitors of MAO-B (selegiline rasagiline), and bioenergetic agents (coenzyme Q), but clinical studies have not fully proven their ability to prevent disease **(Schapira & Olanow, 2004)**

Modern medicine is the science that studies the diagnosis and treatment of symptoms of diseases through the use of medical methods that have been developed over the ages after studies, clinical trials and accurate conclusions, but despite this great progress in this field, its side effects have increased in severity in the past decade, This prompted many patients to return to alternative medicine, or what is known as phytotherapy, as the interest in this type of treatment increased by researchers because it is safer and easier to apply. **(Thomas Sullivan, 2018).**

Several natural agents have been proposed to complete and/or assist the traditional pharmacological agents in the treatment of neurodegenerative disorders, and the general idea of this is provided, among others, by Srivastava and Yadav **(Srivastava, P.; Yadav, R.S,2016).** Their use in NDs is widely reported in the literature **(Lökk *et al*,2010; Shan *et al*,2018; Panda *et al*,2018; Leonoudakis *et al*,2017),** as these products show several different neuroprotective activities. Mitochondrial dysfunction, apoptosis, excitotoxicity, inflammation, oxidative stress, and protein misfolding are among the main neuroprotective targets of natural products **(Leonoudakis *et al*,2017; Bagli *et al* ,2016; Starkov *et al*,2008; Venkatesan, R *et al*,2015; Deshpande, P *et al*,2019).**

Previous studies reported that bioactive polyphenols from herbal drugs played crucial role in the amelioration of neurodegenerative disease mediated by oxidative stress **(G. P. Kumar and F. Khanum,2012)**

Recently, a great number of natural medicinal plants have been tested for their therapeutic properties, showing that the raw extracts or isolated pure compounds from them have more effective properties than the whole plant as an alternative for the treatment of ND. These properties are due mainly to the presence of polyphenols, alkaloids, and terpenes, among others, that are micronutrients produced by plants as secondary metabolites **(T. B. Joseph *et***

***al*,2007; S. Ramos,2007].** There is substantial evidence (epidemiological studies, animal studies, and human clinical trials) that indicates that polyphenols reduce a wide range of pathologies associated with inflammation **(Chiva-Blanch *et al*,2012).** The main mechanisms of polyphenols include their well-characterized antioxidant effects **(Rice-Evans et al,1996; Pignatelli *et al*,2006)**], inhibition of intracellular kinases activity **(Wright *et al*,2010),** binding to cell surface receptors **(Jacobson *et al*,2002),** and modifying cell membrane functions (**Pawlikowska *et al*,2007).**Also, recently the neuroprotective effects of polyphenols have been described in several models of ND and involve mainly signaling pathways mediators **(Zhong *et al*,2009)** modulation of enzymes in neurotransmission **(Kim *et al*,2009)** inhibition of neurotoxicity via ionotropic glutamate receptors **(Chuang *et al*,2013),** antiamyloidogenic **(Ono *et al*,2003)** and anti-inflammatory effects **(Sergent *et al* ,2010)** This review focuses on the plant extracts or compounds isolated from plants that may hold potential in the treatment of the principal ND.

In the context of the search for treatments for nervous breakdown and related diseases, it was concluded that herbal treatment has a pivotal role in reducing these diseases, this is due to the therapeutic properties of medicinal plants as the statistics conducted by the World Health Organization confirmed that there are 21,000 species of plants that have therapeutic properties for neurological diseases **(Yuan H et al, 2016).**

- In this study we will:
  - Research more on the concept, history and branches of phytotherapy.
  - Identify the components of medicinal plants and their therapeutic effects.
  - Knowledge of the structure and organs of the Central nervous system (CNS).
  - Defining the concept of nervous breakdown and determining the mechanism of action of antidepressants.
  - Understand the role of medicinal plants in protecting against neurological diseases and neutralizing their effects.
  - In the end, we tried to provide summaries of all the elements that were touched upon, in addition to providing an analysis of a scientific article on the subject.

Chapter 01:

Generalities on phytotherapy

I-phytotherapy

1-Definition:

Phytotherapy, from the Greek “phyton” meaning(plant) and “therapeuo” meaning (treatment), is the term used to describe therapy with medicinal plants. **(Wichtl M., Anton R, 2003).**

Phytotherapy, also called phytopharmacology or herbalism (herbal medicine), deals with the production of herbal drugs using natural or processed raw materials obtained from medicinal plants (including fungi, apiarian products and some minerals) and their applications in prevention and treatment of diseases. **(Edzard E, 2001).**

Another objective of phytotherapy is to study the properties of medicinal plants, mechanisms of action of herbal drugs and their effects on living organisms, metabolism of active substances contained in them, dosages of individual preparations as well as possible adverse effects or interactions between herbal products and synthetic drugs **(Wichtl M., Anton R,2003).**

2-History of phytotherapy:

Phytotherapy (Herbal medicine) has a long history of evolution in styles and Practice worldwide. In its early stage, herbal medicines were widely utilized over many countries, including Greece and Arabs, medicine in India and traditional Chinese medicine **(Bacher W,1906).**

2.1 Greece old:

The development of phytotherapy began in Europe at the hands of the ancient Greeks, where it was associated with religious rituals and the Greek gods, and with the passage of time the development of this field and its specializations increased, as many doctors appeared, such as Hippocrates (about 460-377 BC), the author of the medical section and the founder of medical ethics **(Saad B *et al.*, 2003).**

2.2 Romans old:

The Romans, in turn, are considered among the first to use herbal medicine, and many doctors and scientists have appeared in this field, the most famous of which is Claudius Galen (second century AD), who created a new field of knowledge, i.e. Galenix, the science

concerned with the production of medicines from fresh or dried plants, in addition to the scientist Pliny the Elder He is another Roman scientist dealing with the properties of medicinal plant materials and the author of several books that included descriptions of more than 1,000 plants and their properties **(Dimitrova Z,1999).**

2.3 Old Arabs:

The ancient Arabs were distinguished by the use of herbal medicine in different ages, as it appeared for the first time in the Sumerian civilization in Iraq and developed with the passage of time up to the eighteenth century, when traditional medicine flourished and doctors' prescriptions included mainly herbal preparations in their raw form in order to treat disease. During that time, the first pharmacy in the world appeared in Baghdad (the capital of Iraq at the present time), where herbal preparations were distributed in the form of oils, tea, syrup, ointments and powders **(Tucakov J, 1990).**

Many Arab doctors have appeared, the most famous of them are Ibn Sina and Al-Razi, who provided amazing medicinal recipes based mainly on herbs **(Tucakov J, 1964).**

3-Principle of phytotherapy:

Phytotherapy depends on the use of plants and their active components, which include (leaves, roots, fruits, flowers, etc.) where these components are concentrated in each part and are subsequently used to treat various diseases. **(Erik Pigani, 2015).**

Scientists and doctors of traditional medicine focus on trying to make the most of the therapeutic properties of medicinal plants by studying their active ingredients and the extent of their positive and negative effects (which are few) on the body, especially skin, glands, hormones, and neurotransmitters, in addition to trying to achieve a common effect for these ingredients by mixing them to restore the balance of biological systems within the patient's body **(Erik Pigani , 2015).**

4 -Interest of phytotherapy:

The interest in herbal medicine has been high since ancient times, and with the development of means and science, the possibility of developing research in this broad field has increased, as it is today competing with modern medicine because of its many benefits **(Anne Prigent, 2018)**, including:

- Side effects are very limited because of the natural composition of medicinal plants
- Medicinal plants are easy to use and inexpensive like medicines and drugs

- ❖ It is used in the formulation of many medicines and drugs
- ❖ Medicinal plants have protective properties from diseases that arise over time
- ❖ Medicinal plants can be used as nutritional supplements for a balanced diet

5-Types of phytotherapy:

5.1 Aromatherapy:

It is a therapeutic method based on the use of aromatic essences plant extracts. These aromatic compounds have different therapeutic properties, according to the plant from which they are extracted. The use of this therapy requires knowledge and a number of precautions **(Kathi Keville. Mindy Green, 2009).**

5.2 Gemmotherapy:

- ❖ Gemmotherapy is a recent therapy, based on the use of buds and young shoots of plants or trees, it is invented by the Belgian doctor Pol Henry, who considers that the buds possess pharmacological virtues superior to those of various parts of a mature plant **(Raiciu, A.D *et al.*,2016).**

This doctor compared the bud to an embryo, which would not only unite the potential of various parts of the plant, namely: roots, stems, leaves, flowers and fruits, but also additional therapeutic properties which would be specific to this plant, this thanks to its wealth of substances potentially active, such as;

- ❖ Polyphenols, especially flavonoids
- ❖ Plant sterols
- ❖ Terpenes
- ❖ Trace elements
- ❖ Vitamins and mineral salts
- ❖ Plant hormones **(Raiciu, A.D *et al.*,2016)**

5.3 Herbalism:

Herbalism is considered to be the oldest and most it uses the plant, whether fresh or dried, whole or only part of the plant. Within this therapy, we find that the preparations are based on methods simple such as: decoction, maceration, and infusion. In addition, these preparations are intended either to be drunk or inhaled, or to be applied to the skin or to be added to the water of a bath and they are also detected in the form of dry plant powder

capsules to swallow. It is the most advantageous form since it preserves components that are fragile **(Tapsell LC ,2006).**

5.4 Homeopathy:

Comes from the Greek word homois=similar, pathos=suffering, that is cure the evil by the evil. Any substance likely to make appear in a healthy individual some symptoms, it is also likely to make disappear in a sick individual similar symptom. Homeopathic dilutions are prepared through the use of fresh plants in alcoholic maceration, these obtained alcoholates are called mother tinctures: it is from these alcoholates that dilutions are prepared Three principles are at the basis of homeopathy: the principle of similarity, the law of individualization, the principle of infinitesimal dilution, There are two types of homeopathic dilutions: Centesimal Hahnemannian Dilution (CH) and Korsakovian dilution (K) **(NCCIH).**

5.5 Chinese herbal medicine;

Chinese herbal medicine, also called Pharmacopoeia, is the use of plants and other natural substances to treat and prevent diseases. Its roots date back to 3 centuries BCE. This discipline is part of Traditional Chinese Medicine (TCM), containing four different branches: acupuncture, Chinese diet, Tui Na massage and energy exercises (Qi Gong and Tai Chi). This practice is now widespread in and is increasingly popular. The Chinese pharmacopoeia contains a few thousand substances, of which about 300 are commonly used medicinal plants **(Lau, T.F *et al.*, 2005).**

5.6 Pharmaceutical phytotherapy;

It is based on the use of products of plant origin derived from extraction followed by dilution in ethyl alcohol or other solvent. The doses of the extracts obtained must be sufficient for the latter to have sustained and rapid action. Thus, they are offered in the form of syrup, drops, suppositories, capsules, lyophilizates, nebulization's, with high concentrations and safety that is not always absolute **(Starng C, 2006).**

6-Indications for phytotherapy:

A main characteristic of plants is the great diversity of therapeutic uses that can be made of them. Each of them (or almost) finds very different fields of application **(Viljoen E *et al.*,2014)** The great richness of components in the same plant explains this phenomenon, it also happens very often that different parts of the same plant act on specific problems Some uses:

- Treatment of joint pain (Harpagophytum, Horsetail)

- Depression and mood disorders (St. John's wort, Crocus)
- Transit problems (Ispaghul)
- Stimulation of the immune system (Echinacea, Pelargonium)
- Blood circulation disorders (Red vine, Horse chestnut)
- Concentration and memory problems (Bacopa, Ginkgo) **(Viljoen E *et al.*,2014)**

II- Medicinal plants

1-Definition

It is any plant that has been shown to contain a number of active substances that have a therapeutic and medical impact on a particular type of disease, or that affect the performance of certain organs in the human or animal body, whether the effect in stimulant or inhibitory (**Mammen Daniel, 2006**), this means that every plant has biologically active compounds called (Plant-active substances) in any part of the plant, in leaves, roots or all plants, so then we can consider the plant a medicinal plant (**Ben-Erik Van Wyk et Michael Wink, 2018**)

The active substances give plants the therapeutic property of certain diseases, and they are also involved in the manufacture of medicines (**Fongang Fotsing Yannick, *et al.*, 2021)**

2- Use of medicinal plants

Generally, the use of medicinal plants is in two forms (**Matthias Hamburger et Kurt Hostettmann, 1991**):

- Raw Form: Such as vegetable oils, herbal extract, soaked.
- Pure shape: through the active substance of the plant.

Plants have been used medically since ancient civilizations, especially in china, today many drugs used and existing contain many active substances plant, and we mention some of the uses of these plants:

Many of the spices and plants that we use in cooking, like ginger, cinnamon, can be used medically (**Abayomi Sofowora, *et al.*, 2013).**

- Used as a medical aesthetic (**Hironori Tsuchiya, 2017**), and as a painkiller (**Charles Marwick, 2005).**

- Used as an ointment against inflammation and skin diseases (**Renata Dawid-Pać, 2013).**
- There is a type of species called fibrous plants have many uses for example in the manufacture of clothing, as well as used medically in the preparation of surgical dressings: such as flax,
- cotton. (**Abayomi Sofowora, *et al.*, 2013).**

Table 01: Examples of some medicinal plants and their uses and effects **(Norman r. Farnsworth *et al*,1985)**

Medicinal Plants	Name	Parts Used	Therapeutic Benefits/ Use	Side Effect/ Over Dose
	Ginkgo	Leaves	-Asthma Treatment -Bronchitis	Ginkgo seeds contain poison thatcan lead to death ifused in large quantities
	Garlic	Garlic Cloves	- Lowers cholesterol and blood pressure -It has antimicrobial effect	-Large amounts of itaffect blood clotting
	Ginseng	Roots	Tonic and aphrodisiac	-Hypertension, Arrhythmia -Avoid using it withwarfarin or heparin (Anticoagulant drugs)
	Silybum marianum (Milk Thistle)	-Especially in the roots, because they contain silymarin	-Treatment of liver disease, high cholesterol -Reducing the growth of cancer cells	-May increase the effects of medicationthat can lower blood sugar levels

Source: Prepared by students based on the article medicinal plants treatment by (**Norman r. Farnsworth *et al.*, 1985**),

3-Components of medicinal plants

What distinguishes medicinal plants from ordinary plants is that one of their components is elements called active substances where these compounds give the therapeutic ability of the plant, as these substances are found in all plants, or in certain parts such as roots, fruits, leaves, seeds, flowers (**Jean Bruneton, 2016**), examples of chemical compounds for active substances: phenolic compounds, glycosides, alkaloids....

4-The active substance of medicinal plants

The active substance is the chemical components in the plant that , such as alkaloids, glycosides, and others, these substances have a therapeutic effect on many diseases where they help to remove symptoms and the healing of the body from the disease, the active substance also enters the synthesis of medicines (**Alaa Hashim Younis Atee, 2020)**

There is a certain time when the proportion of active substances for medicinal plants is high, this is the most appropriate time to collect medicinal plants, there are plants that are advisable to collect their effective parts in the early morning period, in which the concentration of their active substance is high, unlike the evening period (such as plants producing alkaloids), as well as according to the seasons of the year such as Rheum officinal prefers to collect it in the summer season (**Alaa Hashim Younis Atee, 2020**)

4-1-Alkaloids (Component of medicinal plants)

The first origin of the name “Alkaloid” is taken from the Arabic name “ Al-qali”, this word was mentioned in many manuscripts of Arab alchemists such as Al-razi, Ibn sina and others, but The chemist(**Carl friedrich**,**Wilhelm meissner),** was the first to coin the name “Al-qali” to the word “Alkaloid” in the year **1819 (Weizmann.ac.il, site)**

Alkaloids are chemical compounds of natural origin mostly of vegetable origin, but there are also a small number of animals and bacteria that produce alkaloids (**Joanna Kurek, 2019**).

Alkaloids are base compounds and nitrogenous compounds with complex structure, plants produce them with amino acids (**Tristan Richard *et al*., 2013)** ,alkaloids have a therapeutic effect, but they are not specific, because there are different types, each type has a specific effect, among which are sedative alkaloids (morphine), stimulant of the central nervous system (caffeine), as well as anti-

inflammatory, and antiviral, it has been used in the treatment of psychosis and Alzheimer's disease (**Joanna Kurek, 2019**), alkaloids have been classified according to the scientist (**Hegnauer**) into three sections: (**Prasanta Dey *et al* ., and Hyng Sik Kim, 2020**) (**Wojno J *et al.*, 2009).**

A/ True alkaloids: produced by amino acid, heterocyclic.

B/ Proto alkaloids: produced by amino acid, non-heterocyclic.

C/ Pseudo alkaloids: not produced by amino acid, heterocyclic.

They are also structurally classified according to their biological effect, biological composition and chemical nuclei into groups, some of these groups:(**Prasanta Dey *et al.* ,2020**):

- -Quinoléine group: example: Quinine.
- -Isoquinoléine group: example: Berberine
- -Purine group: example: Caffeine **(Hiroshi Ashihara *et al.*, 2013)**
- -Indole group : example : Harmine (**Masanori Somei et Fumio Yamada, 2003**) (**Fresneda etMolina, 2004)**

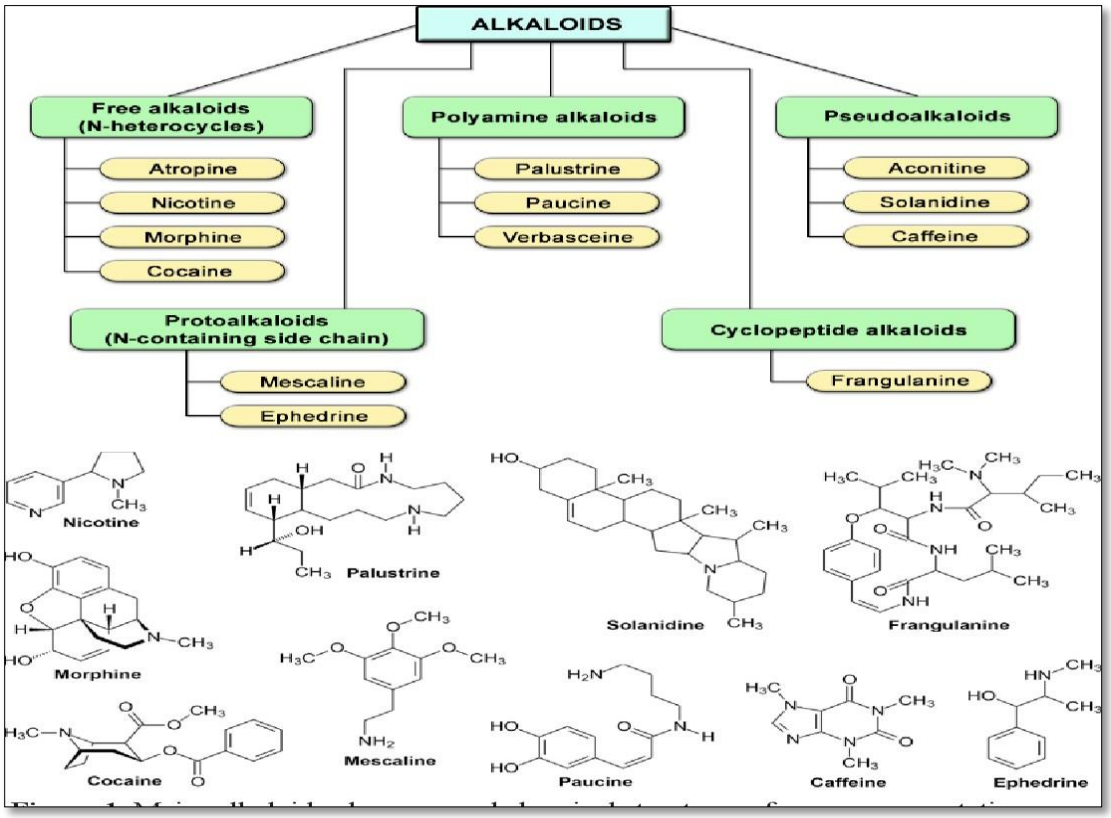

Figure 01: varieties of alkaloids and chemical structures in the types of each class (**Zornistsa Katerova *et al.*, 2013)**

4-2-Flavonoids (component of medicinal plants)

Flavonoids are hydroxyl compounds of natural origin, discovered by the scientist(**Albert Szent-Gyorgyi**) (**Ozan Deveoglu et Recep Karadag, 2019),** are compounds resultingfrom secondary metabolism; it is also one of the largest sections of polyphenol compounds (**Rong Tsao, 2010)**, Flavonoids can be considered as plant pigments that are found in differentparts of the plant such as roots, flowers, and others, they also have the same properties as phenols, so they are weak acidic compounds (**A.N. Panche, *et al.*, 2016**).

Among its importance and roles, it is considered one of the natural compounds that give plants and fruits their distinctive colors, there are also some other roles for Flavonoids: (**Aurelia Scarano *et al.*, 2018**)

- It acts as a filter and protects the plant from UV rays.
- Protect plants from insects and herbivores.
- Flavonoids enter in the stages of plant development, especially the pollination stage.
- It has some therapeutic effects: like anti-inflammatory effects, antispasmodics, anticancer, antiviral, allergy, and high blood pressure, lowering the cholesterol.
- It plays an essential role in the redox (oxidation and reduction) chains (**Shashank Kumar and Abhay K. Pandey, 2013**)

Flavonoids contain **15** carbon atoms, the basic structure of Flavonoids is composed of two benzene rings, **A** and **B**, which are connected to another heterogeneous ring (pyran ring), which contains an oxygen atom, there are also many diverse structural divisions of flavans and 2phenylbenzopyran (**Patricia Hernández-Rodríguez *et al.*, 2019),** Flavonoids are divided into 6 main classes as follows: (**Aurelia Scarano *et al.*, 2018**) (**Ozan Deveoglu et Recep Karadag, 2019) (Nicola Tazzini, 2014):**

1-Flavans
2-Flavones
3-Isoflavones
4-Flavanones
5-Flavonols
6-Anthocyanidins

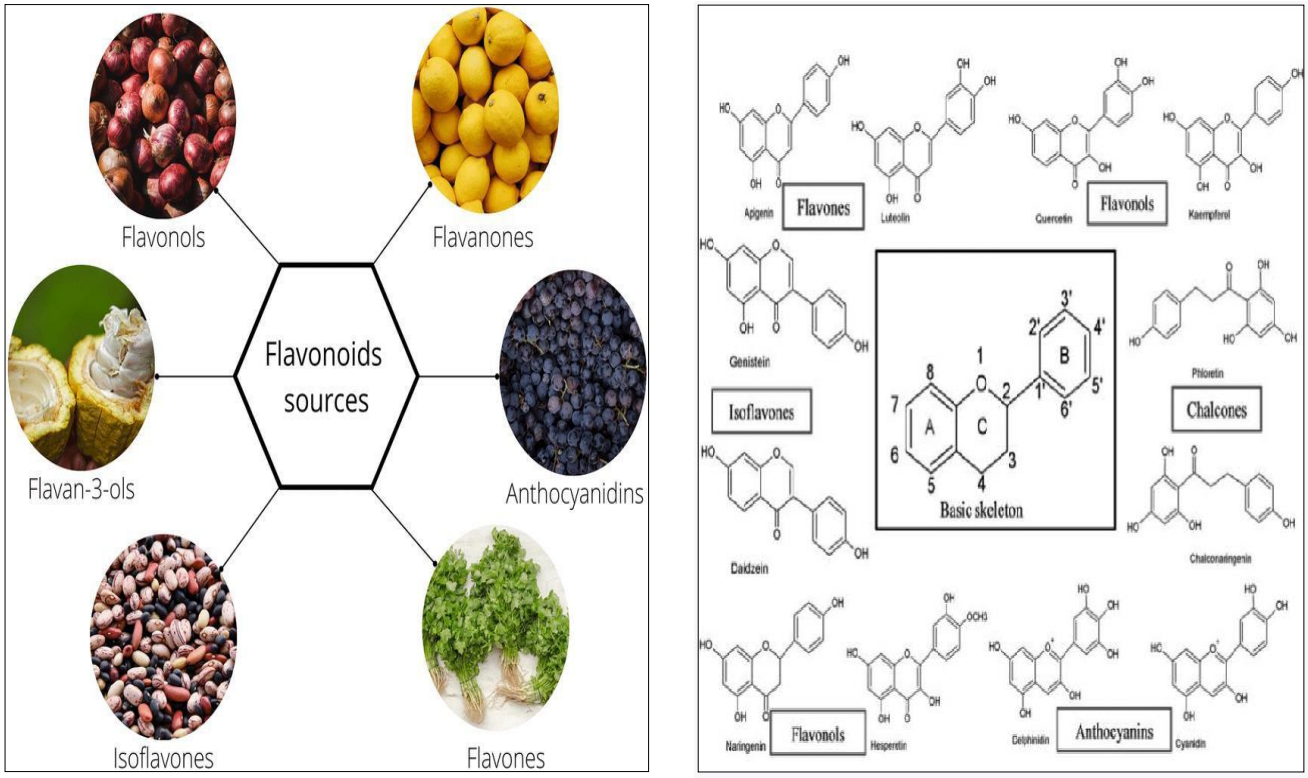

Figure 02: types of flavonoids and their sources **(Shafreena Shaukat Ali *et al.*, 2021) (A.N. Panche *et al.*, 2016)**

4-Phenols (component of medicinal plants)

Phenols are natural compounds in plants, produced by secondary metabolism, it is hydroxyl charcoal compound, and phenols have an aromatic ring with one or more hydroxyl radicals (**Elaine M Aldred BSC (Hons) *et al.*, 2009),** Phenols are always present unitedly, in the form of esters or glycosides one of the most important areas of their production in the plant are protoplasmic bodies such as: chloroplasts, it is synthesized in plants mostly from phenylalanine by the action of phenylalanine ammonia lyse **(PAL) (Andrea Ertani *et al.*, 2016).**

Phenols have many uses, including:

It is important compound in the chemical industry (Considered a raw material in themanufacture of some plastics) (**Minh Tho Nguyen *et al.*, 2003).**

It has pharmacological properties: anti-inflammatory, anti-spasmodic, it is also considered an antioxidant, and it has anti-fungal and anti-bacterial properties, it also protects plants from herbivores (**Donald A. Levin 1976).**

Responsible for the color and special smell of plants and fruits, it is also used industrially as a scented material (Eugenol) (**Atlas of medicinal and aromatic plants in Arabic world, 2012)**

According to **(Abu zaid Al-Shahat 1999)** phenols have four physiological functions: germination, vegetative growth of plants, root growth, and the phenomenon of biological resistance (The ability to resist bacterial and fungal diseases that affect plants), phenols is classified according to hydroxyl groups into: (**Ali Thayer, 2020 chemistry1science, site**)

1-Monohydric phenol: it contains one hydroxyl group.
2-Dihydric phenol: it has two hydroxyl groups.
3-Trihydric phenol: it has three hydroxyl groups.

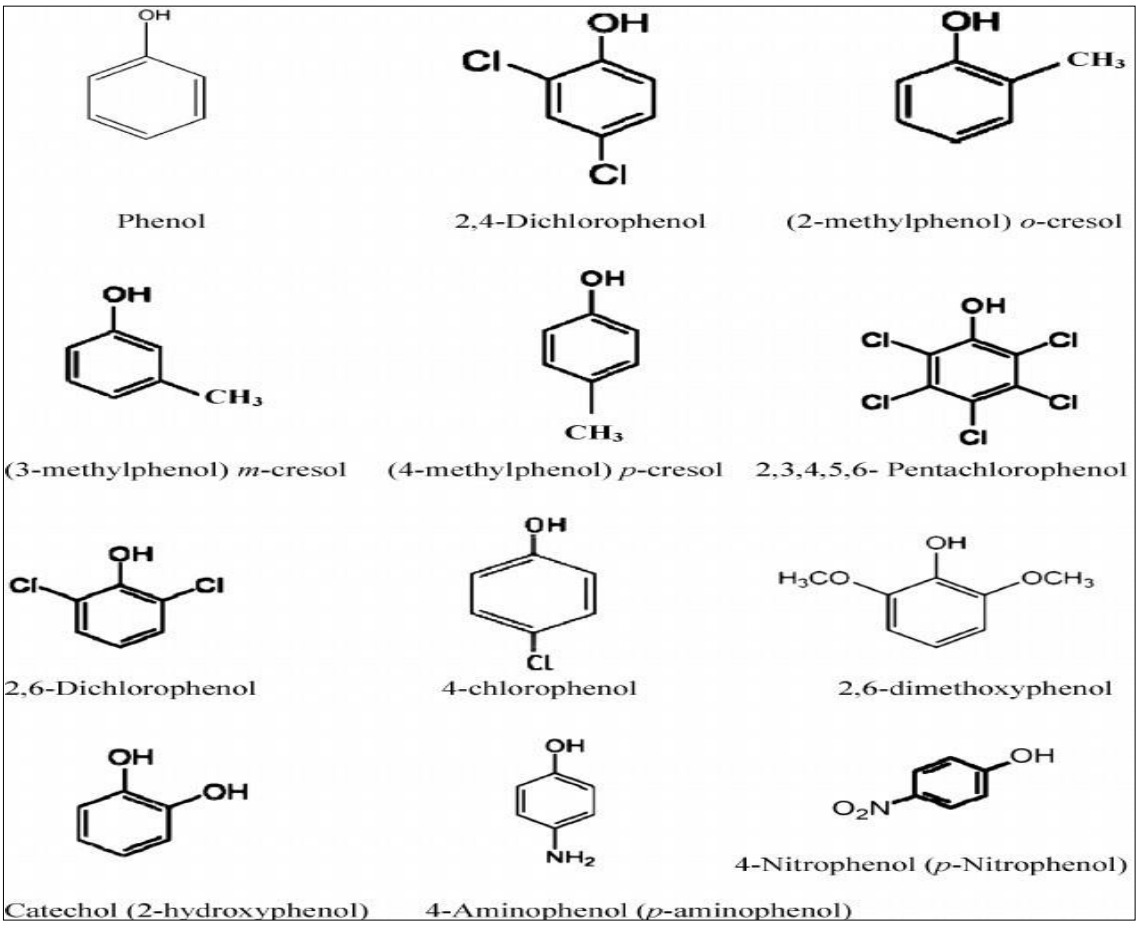

Figure 03: chemical structures of some of the most common phenols **(Muftah El-Nass, 2012)**

5-Action of medicinal plants

Secondary metabolites (SM) produced by plants are very important compounds as they have many roles and characteristics, including those of defending against herbivores and microbes that infect the plant and also possess many biological and pharmacological characteristics (**Michael wink, 2015**).

-As we know that medicinal plants contain many alkaloids, terpenoids and secondary metabolites (SM), they modify and affect an identical molecular target in animals or humans, (**Ben-Erik Van Wyk et Michael wink, 2018**) where these targets are often enzymes or neurotransmitters (**Michael wink, 2015**).

-SM may they have pharmacologically active properties, including antibiotics and antivirals, metabolites can interfere with biological activities because they have more than one active functional group such as epoxides, sh-groups, aldehydes, these groups enable them to form covalent bonds with proteins and peptides, secondary metabolites may also affect the nervous system (**Michael wink,2015**).

-Proteins are the molecules most targeted by secondary metabolites; secondary metabolites have a reactive group, targeting proteins in a non-selective manner, as well as make many bondsand ionic and hydrogen elements, they can also interact with nucleic acids and biofilms, so secondary metabolites are useful as"multi-component drugs" in many diseases **(Michael wink,2015**).

III- Aromatherapy

Definition:

Aromatherapy is the alternative medicine that relies mainly on the essential oils of plants through various methods of application, which gives a positive effect on several diseases.

Aromatherapy appeared in many cultures around the world, so it is one of the oldest methods of treatment in human history, as it appeared in the Egyptian, Indian and Chinese civilizations, where it was used to treat or protect against many diseases previously, such as pain, insomnia, skin allergies, especially nervous ones **(Dioscorides *et al.*, 1959).**

Aromatherapy appeared more than 3500 BC, as the first to use the word "aromatherapy" was the French chemist Maurice Gatifus in 1935, which caught the attention of leading scientists at that time, such as Louis Pasteur **(Lawless, 1997).**

Aromatherapy is a branch of phytotherapy intended to use aromatic plants in the treatment of diseases by exploiting the essential oils present in them (leaves, flowers, bark, sap, fruits, seeds, roots...) **(Corio, 1993).**

Aromatherapy is based on a mixture of essential oils that can create a powerful effect. Today, this type of treatment is widely adopted due to the effectiveness of its results.

2-Proprieties of Aromatherapy:

The characteristics of the aromatherapy process are the properties of the essential oils extracted from plants, here are some plants and their properties of essential oils:

Table 02: properties of plant essential oils **(Garcia Giménez, 2002)**

Plant essential oil	**Proprieties**
cinnamon	Antibacterial, stimulating, antiviral
Celery	Liver tonic, digestive aid, anti-bloating
carnation	Antiseptic, digestive aid
Grapefruit	Anti-Bacterial, Stimulant, Digestive Aid
lavender	Analgesic and antispasmodic
sweet orange	Soothing and anti-bloating
rosemary	Antitussive, antioxidant
mint	Stimulant, aids digestion, and works against migraines

3-Indications and uses of aromatherapy:

Aromatherapy is used to treat several important diseases with self-treatment through inhalation or topical application **(Jean-Pierre Théallet, 2016)**

- Direct inhalation: Where Inhaling essential oils stimulates the smell regions of the brain by affecting the associated limbic system associated with emotions, sensations, and heart rate as providing a pleasant aroma when vaporized, and inhaling them helps to calm nerves **(Milica Acimovic ,2001).**

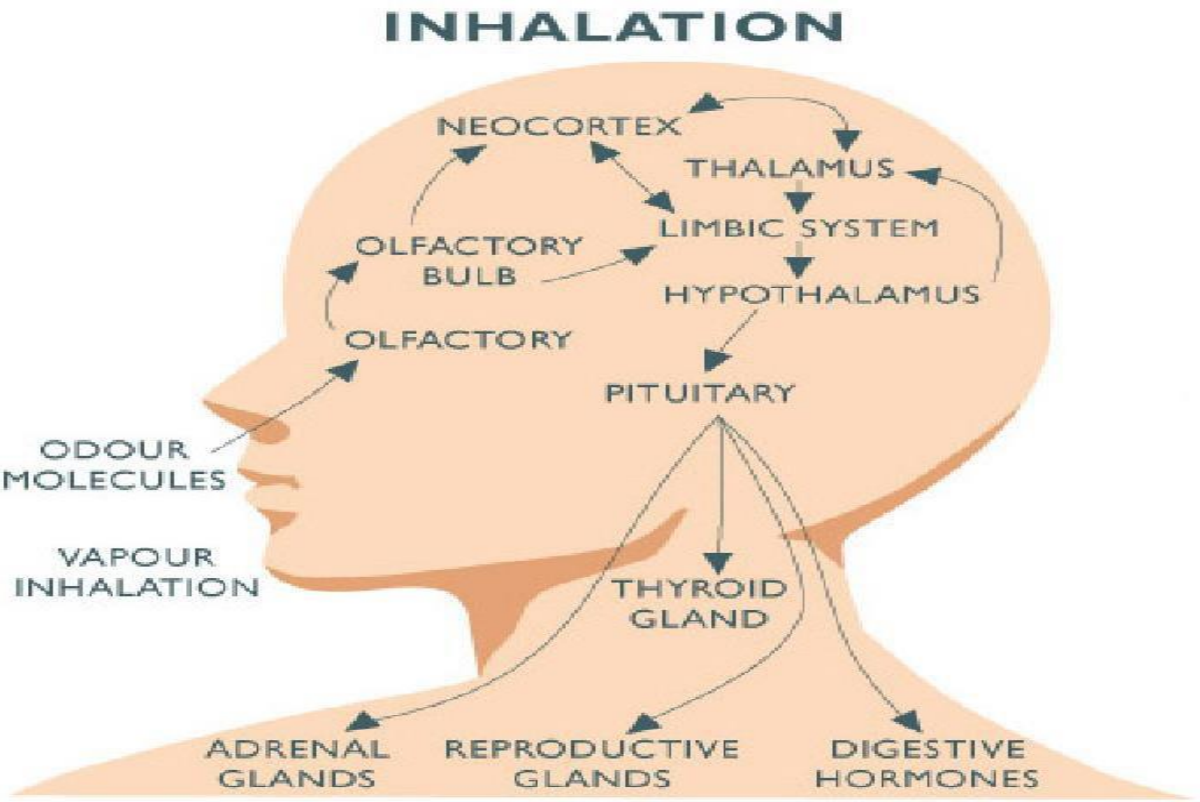

Figure 04: Essential oils direct inhalation **(Store.naturalelements site)**

- Direct application on the body: through massage, where the oils are absorbed through the skin, which leads to the promotion of blood circulation and increased absorption, especially in the areas rich in capillaries of the head and the palms of the hands **(Boem K *et al.*,2012).**

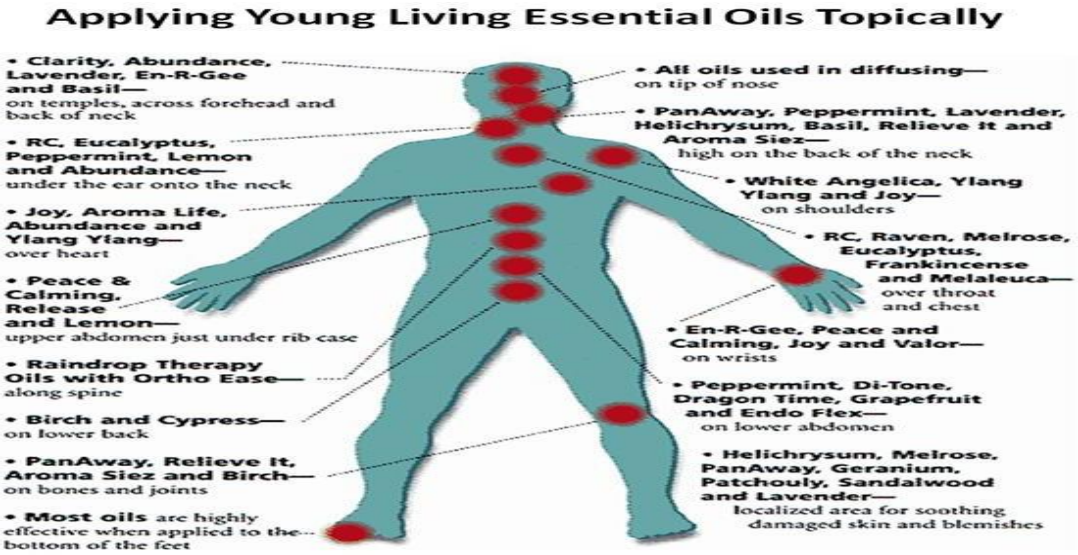

Figure 05: Essential oils topical use areas **(JUGA Complementary Therapies, June 4, 2015)**

-There are several problems and diseases that require the use of aromatherapy, the most important of which are:

- **Treating anxiety, depression and stress:**

Aromatherapy helps to improve the psychological state and mood, and fight anxiety by inhaling essential oils or by using them in massage and physiotherapy **(Basch E *et al.*, 2004).**

- **Headache and migraine treatment:**

The most important studies indicate that aromatherapy has a major role in treating various head diseases through massage with peppermint and violet oil **(Basch E *et al.*, 2004).**

- **Improving immunity and treating infections:**

Aromatherapy helps relieve fungal or bacterial infections through the composition of essential oils that contain sterile elements such as lemon oil **(Gnatta J.R, 2015).**

- **Rebalancing the hormones:**

Aromatherapy has shown great effectiveness with regard to diseases related to glands and hormones, as experiments have confirmed that essential oils that are used in aromatherapy have effectively contributed to rebalancing hormones such as estrogen, testosterone and progesterone **(Lis-Balchin, 1997).**

- **Promote healthy hair and skin:**

Aromatherapy is a wide field that also includes the field of cosmetics, where essential oils are included in the composition of most cosmetics that protect against aging, hair loss and eczema **(Lucia, A.; Guzman, E,2021)**

4- Types of aromatherapy:

Aromatherapy is divided into five classifications according to the desired purpose of its use and the elements used in it.

4-1-Massage aromatherapy:

This process is based on massaging the body with essential oils, and these oils are absorbed through the pores of the skin to affect the limbic system **(Soden K, 2004).**

4-2-Cosmetic aromatherapy:

In this field, we use hair and skin preparations, cleaning and moisturizing the skin and strengthening the hair through the effective effect of the essential oils that are used, such as lavender oil and cinnamon oil **(Ziosi P, 2010).**

4-3-Medical aromatherapy:

With the progress and development of aromatherapy in the modern era, Dr. Rene-Maurice Gatte-fosse was able to discover several positive effects of essential oils, as he used them during some difficult surgeries **(Maeda K, Ito T, Shioda S, 2012).**

4-4-Psycho-aromatherapy:

It takes care of the psychological aspect of the patient using essential oils to give him a feeling of happiness and studies the positive and negative effects of smell on humans and how these effects occur and to what extent they can be dangerous or beneficial. **(Perry N, Perry E, 2006)**

5- Essential oils:

Aromatherapy depends mainly on plants, which are a primary source in the manufacture of medicines and therapeutic drugs **(T. Dunning Aromatherapy, 2013)**, but why plants?

Since ancient times, man has used plants as a source of food and livelihood and cosmetics, perfumes and preservation, and with the succession of ages he discovered that they have important therapeutic effects, as he used their extracts to treat some diseases and injuries **(A. Krishna *et al.*, 2000)**, so what are these extracts?

These extracts are known today as essential oils, as they are used to improving mental and physical health. They are used in the manufacture of most of the medicines and preparations that we use today to treat various diseases and health problems **(D. Jimbo *et al.*, 2009).**

5-1- Definition of essential oils:

Essential oils are oily extracts extracted from plants or some of their parts (leaves, roots, bark...) through either mechanical pressure or distillation **(K.P. Svoboda, S.G. Deans, 1995)**

They are characterized by their high concentration and strong odor consisting of hundreds of small-sized aromatic molecules, which facilitates their absorption from the body, whether

through massage or inhalation. It also facilitates the metabolism process. **(K.P. Svoboda, S.G. Deans, 1995)**

5-2- composition and physicochemical properties of essential oils:

Essential oils consist of several molecules in different proportions called aromatic**(Adams, R.P, 2007)**, which control the properties of the oil and the mechanism of its effect on the organic matter **(Adams, R.P, 2007)**, as well as the degree of its toxicity, which contributed to the increased interest in these components. So, what are the common components between essential oils? What are its physical and chemical properties?

5-2-1-compositions of essential oils:

A-Terpenes

Terpenes represent the most important components of essential oils that determine the smell of many plants and herbs derived from two isoprene units, which are a huge group of hydrocarbons C10H16 they are decongestants for the respiratory and lymphatic systems some examples of terpenes : citral,phytol,rubber…… **(Generalić Mekinić *et al.*, 2016).**

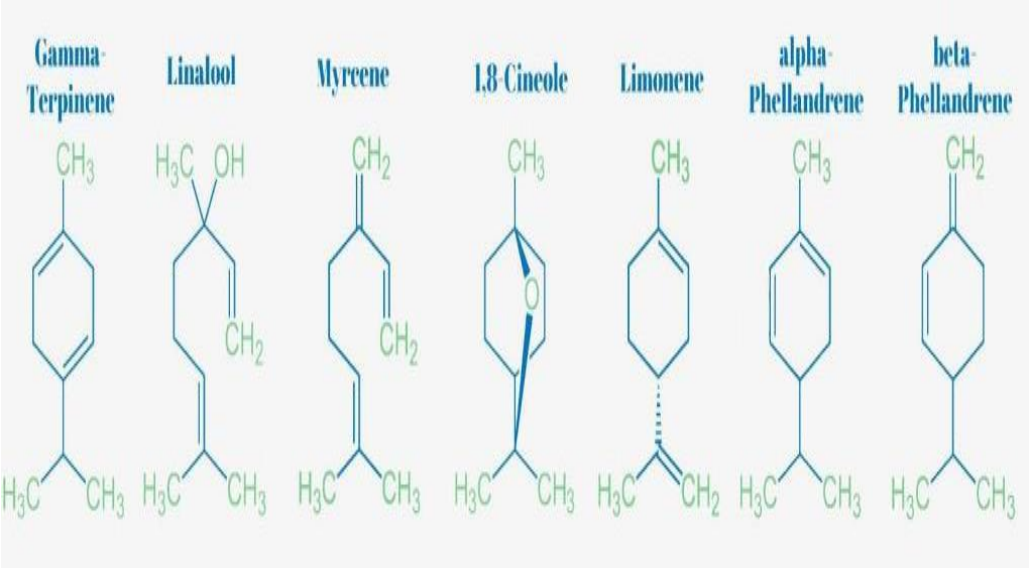

Figure 06: some examples of terpenes structures **(botanica testing site)**

B- Alcohol:

Alcohol is one of the most important components of essential oils and the best anti-infective. It is also considered a stimulant for the immune and nervous systems and an intervention in the treatment of bacterial, bacterial and fungal diseases **(Miyazawa, M, 1997).**

C-Esters:

Esters arise from the union of an alcohol and an acid with the loss of water, and are salts of organic acids. They have several antispasmodic, anti-inflammatory, sedative, analgesic and tonic properties **(Schiller C, Schiller D, 1994).**

D-Aldehydes:

Aldehydes are anti-infective, antiviral, antimicrobial and antifungal. They are irritating to the skin and should be diluted. Aldehydes are hydrocarbons, the least stable components of essential oils **(Schiller C, Schiller D, 1994).**

5-2-2- physicochemical properties of essential oils:

Essential oils share their physicochemical properties, and these properties constitute a homogeneous group among them. The most important of these characteristics are the following:

- Essential oils are naturally liquid (**Krishna A *et al.*,2000**)
- Essential oils have a beautiful scent and differ from one oil to another**(Wildwood C,1996)**
- Soluble in alcohols of high alcoholic strength and in most organic solvents – **(Radulović, N.S *et al.*,2015)**
- Highly alterable, sensitive to oxidation and tend to polymerize **(Fisher, K. & Phillips, 2008)**
- Low density for essential oils with a high monoterpene content **(Berti, M *et al.*, 2008).**

This table represents the physical properties of some components of essential oils

Table 03: Components of essential oils and their physical properties

E.O components	Chemical Formula	Molecular Weight	Boiling point C0	Refractive index (20 C0)
Ketones alcohols Camphor	C10H16O	152.23	204	-
Monoterpene D-Limonene	C10H16	136.23	175.4	1.473
g-Terpinène	C10H16	136.23	183	1.474
Terpenic oxides 1,8-Cineole	C10H18O	154.25	176	1.457
Oxygenated sesquiterpenes a-Bisabolol	C15H26O	222.37	153	1.496
Terpenic oxides Cis-Rose oxide	C10H18O	154.25	70–71	1.454
Cinnamaldehyde	C9H8O	132.16	248–250	1.621

5-3-Production and extraction of essential oils:

Essential oils are used in many fields, which requires their production on an ongoing basis due to the need for their benefits according to use**(Baris.O, 2006)**, which made the methods of extracting them develop over time to obtain the highest possible quality of these oils**(Donelian *et al.*, 2009),** so what are these methods, and how are they applied?

5-3-1-Methods for extracting essential oils:

There are several ways to extract essential oils from plants, where ancient techniques are used largely to obtain the best possible results to make more use of the obtained oil.

❖ **Hydro distillation:**

This method is one of the oldest methods used and easy to apply **(Meyer-Warnod *et al.*, 1984),** which aims to separate the essential oil, where the plant material is placed in a place designated for heating, then add a large amount of water and then the mixture is heated well until the oils evaporate And the water passes to the condenser, so the oil floats on top of the water, which facilitates the process of separating them.

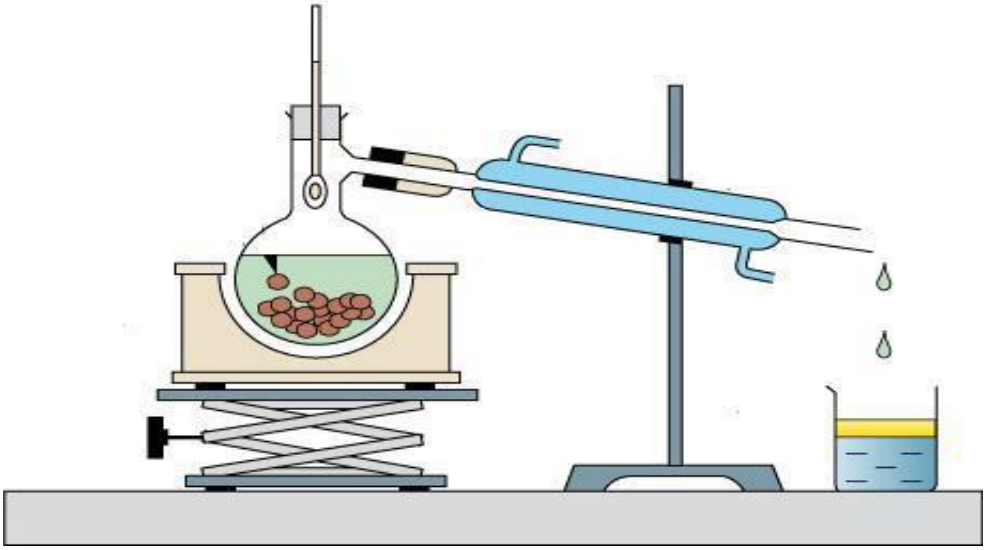

Figure 07: Hydro distillation method for extracting essential oils (**Hesham H. A. Rassem *et al.*, 2016)**

❖ **Steam Distillation:**

This method is used for plants affected by heating **(Fahlbusch *et al.*, 2003).** The plant material is placed in the alembic without the use of water. Where is the steam introduced into the alembic, and it passes through the cavities of the plant material, liberating the oil particles and mixing with the steam, then we condense them in the condenser and separate them inside a special separator and extract the essential oil we want **(Rai R. and B Suresh B, 2004).**

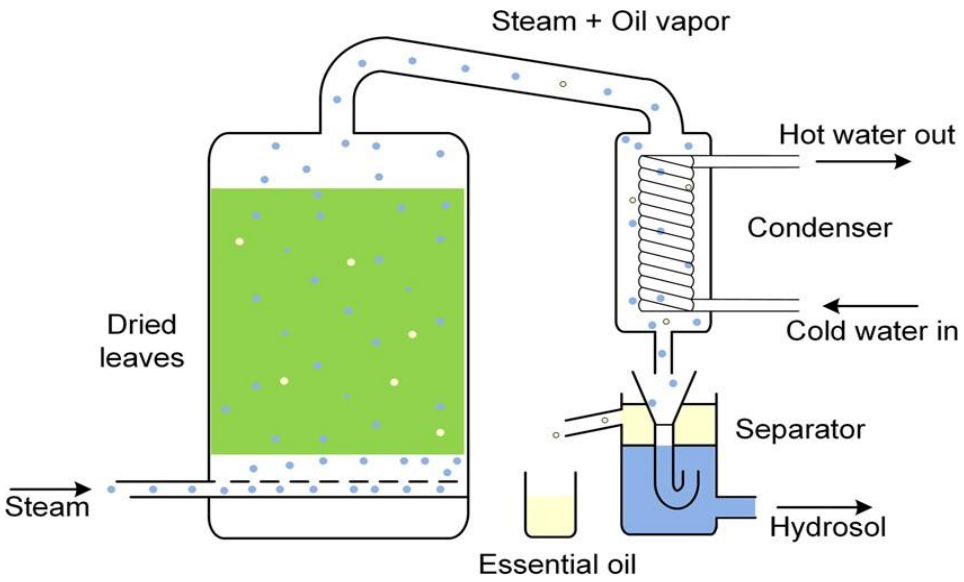

Figure 08: Steam Distillation method for extracting essential oils **(Werther, J *et al.*, 2000)**

❖ **Solvent Extraction:**

- -In this process, we use solvents to extract essential oils **(Chrissie *et al.*, 1996)** such as benzene or ethanol, where the solvent absorbs the essential oil after the solvent mixes with the plant matter **(Dawidowicz *et al.*,2008).**
- -Then we separate the components of the mixture through distillation using alcohol at a low temperature, then condensation and keep the essential oil **(Harwood *et al.*, 1989).**

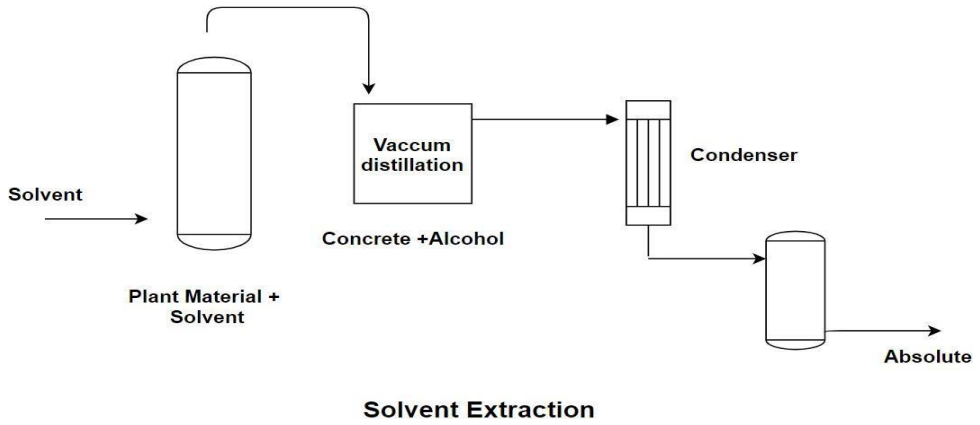

Figure 09: Solvent Extraction method for extracting essential oils **(olicaworld website)**

❖ **Cold Pressing:**

In this process, strong pressure is applied to the plant to extract the pulp, including the essential oil, and then separate it from the plant material through centrifugation **(Arnould *et al*., 1981).**

There are several other types of processes for extracting essential oils from plants Enfleurage, Microwave extraction, Supercritical Fluid Extraction (SFE), Carbon Dioxide (CO2) Extraction… **(Dick and Starmans,1996).**

5-4-Types of essential oils:

There are several types of essential oils that differ according to their composition and therapeutic effect. We can classify more than 90 different types of them. This is a list of the most used types of essential oils in various fields and their source. **(Georges Sens-Olive, 1979).**

Table: most used types of essential oils **(Georges Sens-Olive, 1979)**

Essential oils	Their source
Agar oil	Agar wood
Angelica root oil	Angelica archangelica.
Asafoetida oil	Myroxylon
Black pepper oil	Piper nigrum
Calamodin oil	Citrus tree
Frankincense oil	Trees of the genus Boswellia
Ginger oil	Ginger tree
Sandalwood oil	Trees in the genus Santalum
Sassafras oil	Deciduous trees

5-5- Toxic kinetics of essential oils:

Essential oils have a complex composition, their movement within the organic matter is studied through specific stages, which are

5-5-1-Routes of administration of essential oils:

The main routes of administration of essential oils are the oral route, the rectal route, the cutaneous route and the respiratory route so the choice of route of administration varies according to the patient's age, location, also solubility or flavor properties of the oil, or its effect on both the nervous and digestive systems **(Schmitt.F, 2010).**

A-Oral route:

In the oral route, essential oils are given through a support, either solid (sugar cubes or capsule) or liquid (solution or syrup), but the oral route does not work for all essential oils because some are toxic. **(Zimmermann I, 1995).**

The dosage varies according to the type of treatment, whether it is preventive or curative, and it may be a drop or more, as well as according to the properties of the oil**. (Zimmermann I, 1995).**

The duration of treatment varies depending on the extent of the organic response to the effects of the oil and may be up to ten days. Oils may damage the stomach **(Zimmermann I, 1995).**

B-Pulmonary route:

The pulmonary or respiratory route allows local and systemic action to cross the essential oils. There are four routes of administration through this route:

- **Dry inhalation:** Drops of the essential oil are placed in a dry thing such as a handkerchief and then inhaled directly **(Mailhebiau *et al.*, 1992).**
- **Wet inhalation:** The essential oil is placed in boiling water and then breathed in for about ten minutes. **(Falk, A.A, 1990).**
- **Aerosol**: The essential oil is inhaled in the form of minute droplets to reach the deep respiratory tract. This method requires medical supervision **(B. A. Forbes *et al.*,2007)**
- **Air diffusion**: Air quality is improved by exploiting the antimicrobial properties of essential oils, but some of them may harm the lung, especially asthmatic patients **(Mailhebiau *et al.*, 1992).**

C- Cutaneous route: This route is considered the most widely used, as oils are diluted before using them to facilitate their passage through the skin, especially oils rich in phenols and aldehydes, where their medical use is for about eight hours **(Faucon, M., Lobstein. A, 2015).**

It can also be combined with ointments or dissolved to make aromatic baths, where essential oils consist of skin-loving and easy-to-pass particles, but the risk of skin allergy remains, so it must be used well whether it is used locally through the skin or regionally through the joints or nerves **(Godin B *et al.*, 2007).**

d- Rectal route: The rectal route allows for good diffusion of the active molecules, either through topical or systemic use. Essential oils are combined with suppositories. This route is recommended especially for people who have difficulty swallowing oils through the mouth. **(Javorka, K *et al.*, 1980).**

5-5-2-Distribution of essential oils:

The distribution of the molecules that make up essential oils is according to their physical and chemical properties, whereby the fat-soluble molecules are rapidly circulating, especially in the brain and liver. As for the blood, the diffusion depends on the free part present in the blood, as the higher it rises, the higher the passage of the molecule where the plasma proteins are bound With the essential oil molecules, especially the albumin protein, which is the most important protein in the blood plasma, and the blood vessels have the ability to facilitate the passage of essential oil molecules to the main organs of the kidneys, liver and lungs. **(Franchomme, 2015).**

5-5-3- metabolism of essential oils:

Biotransformation of aromatic molecules occurs aim of making these substances more hydrophilic and thus accelerating renal elimination, the liver is the most important organ in the metabolism process, then the kidneys, lungs and mucous membrane... **(Miyazawa &Chan, 2002).**Several changes occur to the metabolite during the metabolism process through several reactions and stages when biotransformation reactions are divided into 2 phases:

- **Phase I reactions**:

That make the molecules more hydrophilic by adding polar groups so we find in this phase the hydrolysis reactions the esters will thus give alcohols and carboxylic acids), oxidation (which causes the addition of oxygen, nitrogen or sulfur atoms) and reduction **(pharmacomedicale.org, 2016).**

Oxidation reactions take place mainly through enzymatic compounds called Cytochromes (CYP450); it is present in high amounts in the microsomes of the liver where these

compounds can oxidize a wide range of aromatic molecules found in essential oils such as limonene through an enzyme called (CYP2C19) … **(Millet, 1981).**

- **Phase II reactions**

Metabolized substances will be fixed on very polar endogenous molecules which will make the whole sufficiently hydrophilic to be able to be eliminated these molecules, including glucuronic acid, glycine and sulfate, will respectively give reactions of glucuronoconjugation, glycoconjugation and sulphoconjugation **(Miyazawa &Chan, 2002).**

5-5-4 Elimination of essential oils:

Exogenous substances are eliminated by the kidneys, liver, lungs and skin but the kidneys are the most important in this process **(Kohlert. D, 2002).**

Aromatic compounds are rapidly eliminated through the kidney despite the greater attraction to adipose tissue **(Kohlert. D, 2002).**

5-6 The role of essential oils against neurological diseases:

-The nervous system is one of the complex systems responsible for many important functions in the body, but sometimes its efficiency may decrease or stop completely due to neurological diseases, which are a defect that affects one part of the nervous system, which makes the patient unable to perform his activities normally and poses a great danger to the human life. (**Wang Z.J., Levinson S.R, 2014).**

- Several symptoms associated with neurological diseases appear, such as memory loss, vision disturbances, tremors, chronic epilepsy and difficulty of speaking **(Bagetta *et al.*, 2010).**

- The treatment of neurological diseases varies according to the disease and its cause, including surgery, neurological rehabilitation, medical drugs, or aromatherapy using essential oils **(Wang Z.J., Levinson S.R, 2014).**

- Essential oils today play a very important role in the treatment of various neurological diseases because of their great impact on different parts of the nervous system Because of their constituent elements by three actions:

- Biochemical activity: the biochemical receptors of our body capture the molecules of essential oils, which leads to a therapeutic action **(Faturi *et al.*, 2010).**

- Energy activity: essential oils exchange electrons with the environment in which they are found, which modifies energy flows **(Faturi *et al.*, 2010).**
- Informational activity: the scent of essential oils acts on the brain by triggering psychological and physiological reactions **(Faturi *et al.*, 2010).**

-These are some components of essential oils and their effect in the treatment of neurological diseases:

a-The essential oils that contain 1, 8-Cineole which is considered as antinociceptive, smooth muscle relaxant and neuronal excitant by reducing the excitability of peripheral neurons by blocking the voltage-dependent current Na + and inhibiting potassium channels (**Ferreira-da-Silva *et al.*, 2015).**

b-The essential oils that contain 1-Nitro-2-phenylethane which have hypnotic, anti-convulsant and anxiolytic effects by the inhibition of contractile events that are clearly independent of Ca2+ influx (**Oyemitan, 2013).**

c-The essential oils that contain Menthol, which have anticonvulsant, antinociceptive and anesthetic activities by the agonist of GABAA receptors hippocampal neurons (**Kawasaki *et al.*, 2013).**

d-The protective effect of lavender oil against cerebral ischemia as linalool inhibits the release of acetylcholine and alters the function of the channel at the neuromuscular junction (**Van Bred erode, 2016).**

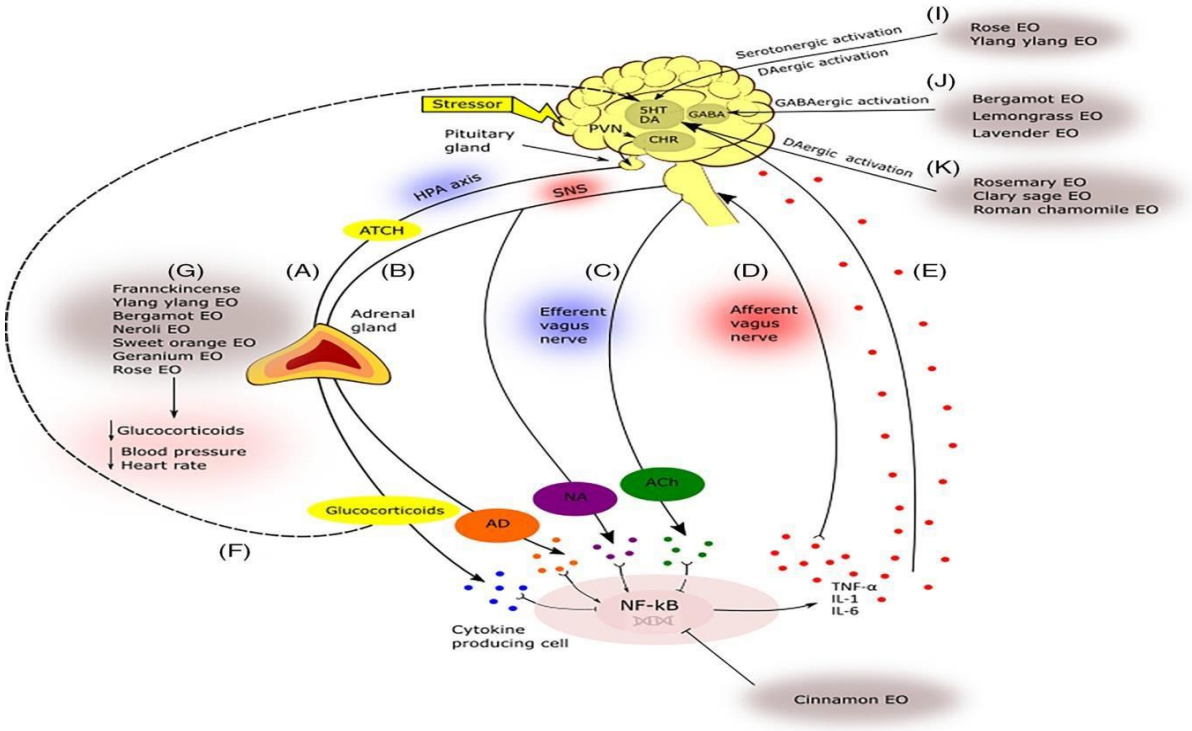

Figure 10: Effects of essential oils on central nervous system (**Phytotherapy Research site august, 29, 2020)**

Chapter 02:
Neurological disorder

I- Central nervous system (CNS)

Group of cells specialized in regulating all sensory and motor processes within the body and transmitting signals between them, such as speech, memory, sensation and feeling **(Galli R *et al.*, 2003).**

1-General organization of the nervous system

The nervous system is divided into two main parts: the central nervous system, which includes the brain and spinal cord, and the peripheral nervous system, which includes all the other nerves of the body **(Menche N, 2012).**

1-1-Anatomy of the central nervous system

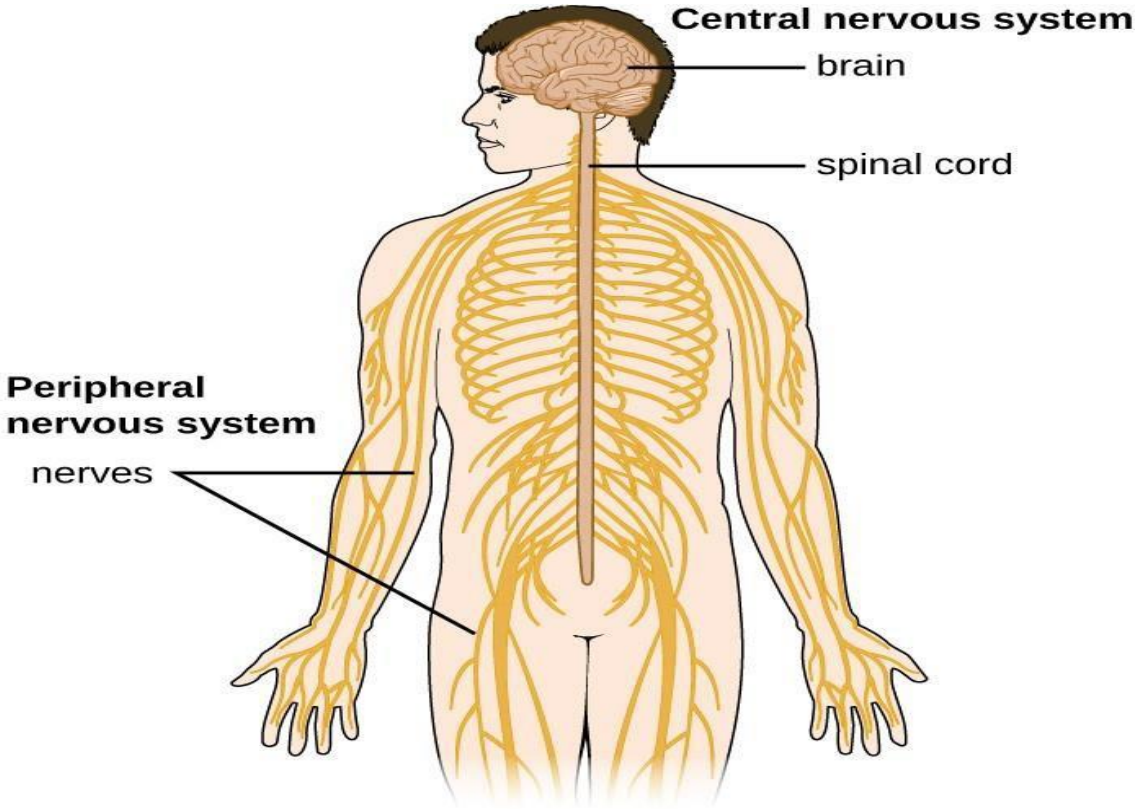

Figure 11: The essential components of the human nervous system: central nervous system (CNS) and peripheral nervous system (PNS) **(Yuki *et al.*, 2012)**

II- Brain

The brain is the main organ in the nervous system and the most complex organ in the body because it consists of more than 100 billion neurons and weighs about 1.5 kilograms **(Nolte, J, 2002).**

1-External Morphology of the Brain

The brain consists of a group of specialized nerves and blood vessels that include neurons and glial cells. It is made up of about 60 percent of fats and 40 percent distributed over proteins, carbohydrates and salts **(Nolte, J, 2002).**

The brain consists mainly of three main parts, the cerebrum, which fills the largest part of the skull, the cerebellum, which is located under the cerebrum, and the brain stem located under the cerebrum and in front of the cerebellum. It connects the brain and spinal cord (**Allen, N. J., & Barres, B. A, 2005).**

1-1 Anatomy of the brain

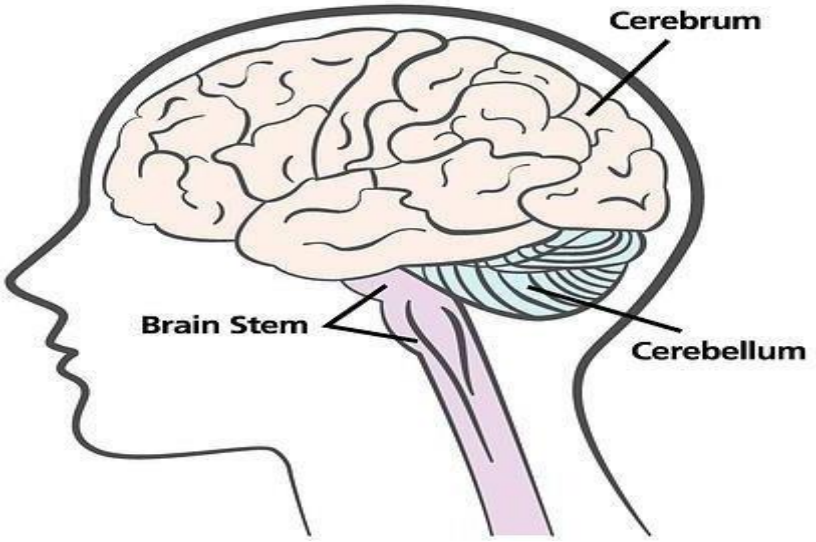

Figure 12: The three main parts of the brain **(Nolte, J, 2002)**

1-1-1-Cerebrum

It is the largest part of the brain, accounting for two-thirds of its total weight. It is formed from the right and left cerebral hemispheres separated by an interstitial fissure, forming what is known as the corpus callosum, which transmits nerve messages between the two hemispheres **(Schutter, D. J., & van Honk, 2005).**

The hemispheres consist of white matter, myelinated nerve fibers, and the periphery of the gray matter, and are divided into a group of lobes, each with its own function **(Schutter, D. J., & van Honk, 2005).**

- **Frontal lobe:**

It is located in the front of the brain and is the largest lobe. It performs many functions, the most important of which are movement, planning, attention, and controlling emotions **(Schmahmann, J. D., & Pandya, D. N, 2006).**

- **Parietal lobe:**

Located behind the frontal lobes, its task is to transmit sensory messages to the rest of the brain, such as temperature, taste, and touch **(Schutter, D. J., & van Honk, 2005)**

- **Occipital lobe:**

It is located in the back of the brain and is responsible for visual and color processing **(Schmahmann, J. D., & Pandya, D. N, 2006).**

- **Temporal lobe:**

It is located near the ear and on the side of the brain. Its task is to store memories and combine them with sensory actions such as smell **(Ramachandran, V. S. (Ed.), 2002).**

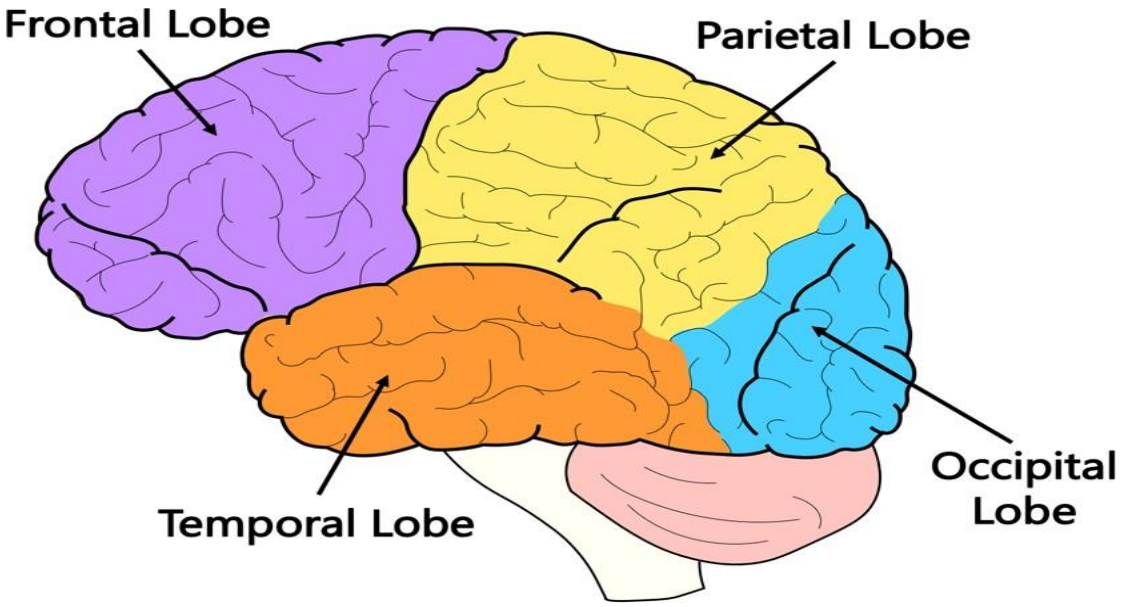

Figure 13: The location of the four lobes in the brain **(Schutter, D. J., & van Honk, 2005)**

1-1-2- Cerebellum

It is a major part of the brain located near the occipital lobe, preferred over the brain by the dura fold, which accounts for 10 percent of the total weight of the brain. More than half of the brain's neurons are concentrated inside it. It is responsible for motor skills and body balance (**Barton RA, 2014).**

1-1-3-Brainstem

A part goes below both the cerebrum and the cerebellum and is connected to the spinal cord through which all the information of the brain passes to the body and vice versa.

It is formed by a group of cranial nerves that control the movement of the eyes, neck, face, swallowing and taste. It consists of the midbrain responsible for eye movement and vision, in addition to the pons that connect the parts of the brain, and finally the medulla oblongata, which controls breathing and blood pressure.

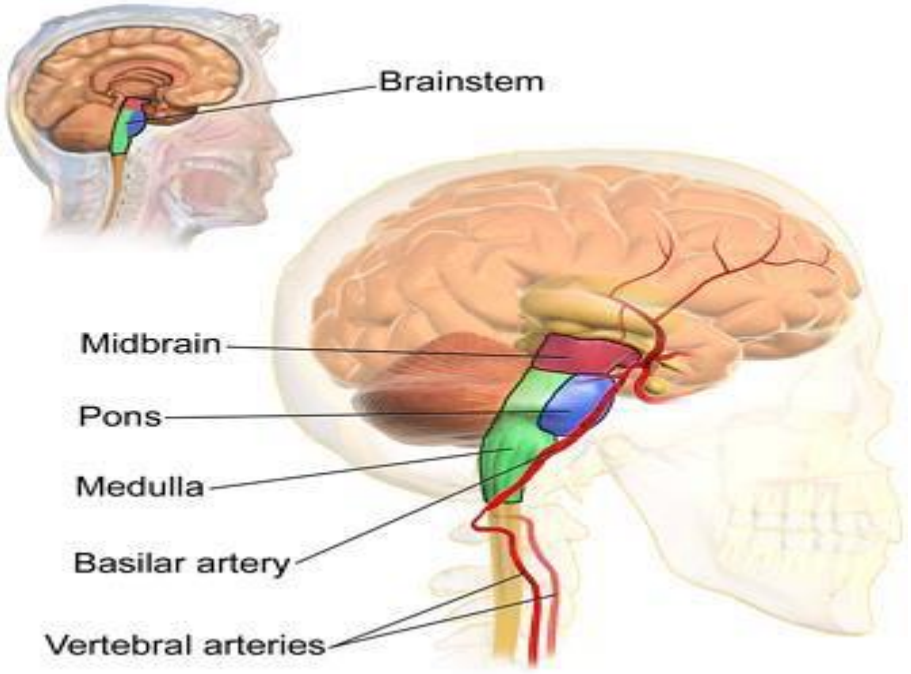

Figure 14: Brainstem structure **(Bruce Blaus)**

1-1-4-Diencephalon

It is located in the depth of the brain and regulates the relationship between the glandular system and the nervous system **(Bergquist H., Kallen B, 1954)**.It consists of the thalamus, which regulates sleep and nerve signals, and the hypothalamus, which connects the limbic system and the brain, responsible for sensations, in addition to the hypothalamus, which

constitutes the unit of sending nerve signals to the pituitary gland and processing involuntary nervous messages which comes from the spinal cord and regulates important processes such as sleep, eating and secretion of hormones **(Torrico TJ, 2005).**

2- Hypothalamus

It is a conical region located between the pituitary gland and the hypothalamus. It works by stimulating the production of hormones and many vital processes within the body, and accounts for 1 percent of the brain's total weight. Its importance lies in maintaining the stability of body systems such as temperature, hunger and thirst by affecting the endocrine glands after interaction with the pituitary gland **(Chrousos GP,1995).**

The hypothalamus is connected to the pituitary gland by many motor and nerve pathways. The median eminence, which is the posterior part of this region, contains a large number of secretory nerve endings that connect them and contains the mammillary bodies, optic chiasm and the third ventricle **(Braak H, Braak E, 1992).**

It is divided into 3 regions, first the front, which is located above the meeting point of the human. This area secretes many hormones, such as corticotropin and somatostatin. It is also divided into two side and middle parts that work to balance the body's energy, sleep and memory **(Cocco C *et al.*, 2017).**

Among the most important functions of this gland are:

- Create a balance between hunger and satiety **(Lechan RM, Toni R, 2016).**
- Regulating blood pressure and body temperature **(Persani L, 2012).**
- Modify emotions such as fear and joy **(Stagkourakis S *et al.*, 2019).**
- Regulating the work of the digestive system, intestines and stomach **(Persani L, 2012).**
- Develop learning and memory skills **(Lechan RM, Toni R, 2016).**
- Balancing body fluids **(Stagkourakis S *et al.*, 2019).**
- Control of appetite **(Stagkourakis S *et al.*, 2019).**

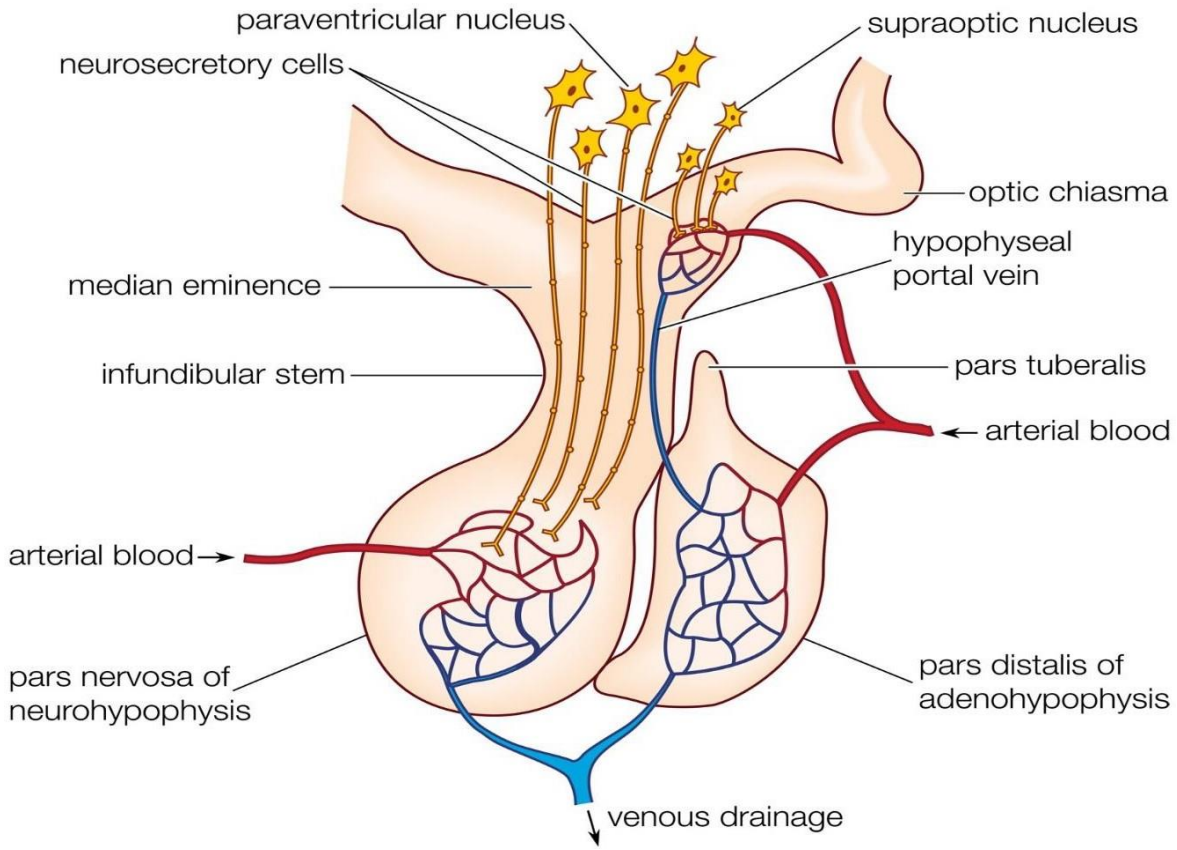

Figure 15: Parts of the hypothalamus **(Andrew V. Schally Roger Guillemin)**

III-Limbic system

1-Pineal gland

1-1 Generality

This name was given to the pineal gland because of its similarity in shape to a pine cone (Latin pineas), (**Kenneth L, Becker *et al.*, 2001**), it is also called conarium, pineal organ, apricot cerebral, it is an endocrine organ, located behind the third cerebral ventricle in the center of brain behind eyes**(Charles H.Emerson, 2020).**

It was the first mentioned medically by the Greek physician **(Claudius galenus)** in the second century; the French philosopher **(Rene Descartes)** also defined it in the **17**st century as **(seat of the soul),** but science has not yet proven the ideas that the secretions of this gland have a major role in sensation and perception **(Charles H.Emerson, 2020),** in **1958** a group of

researchers **(AaronB. Lerner et al., At Yale University)** they isolated and named the main hormone secreted by the pineal gland (**melatonin**), they extracted it from the pineal gland of a cow **(Jeremy pearce, 2007)**

1-2 Physiology of the Pineal Gland and Melatonin

The pineal gland is as small as a pea (**100-150 mg**), and it's less than **1cm** long, rich in adrenergic nerves (**epinephrine**), its function is to receive information about the state of dark-light cycle from the environment and transmit information in order to produce and secrete melatonin (derived from tryptophan), this hormone is secreted during the dark period, where optical information is sent from retina to the suprachiasmatic nucleus (**SCN**) (mammalian "clock" generation system), and from there to the hypothalamus, if this light signal is positive, the SCN secretes gamma-amino butyric acid this acid is responsible for inhibiting neurons in the paraventricular nucleus (**PVN**), when PVN cells are inhibited, then there is no signal sent to the pineal gland, and thus melatonin is no secreted from it (in the light), on the contrary, in the dark, where melatonin is synthesized and secreted (**Aulinas Anna, 2019**).

Melatonin has other roles including being instrumental in modulating inflammatory responses (**Eli Gilad *et al*., 1998),(Beni *et al*., 2003**), melatonin is also involved in protecting cells and the reproductive system, and neuroprotection, in addition to its primary role in regulating the daily regime and determining sleep patterns (**Aulinas Anna, 2019**).

The pineal gland secretes other hormones such as the precursors to melatonin, and also serotonin, which is derived from alkaloid tryptamine, the pineal gland also produces neurosteroids, despite the development of technologies in the **21**st century, the effects and properties of the pineal gland, especially melatonin, are not fully known, it is likely that it has other roles in the body that we do not know yet (**Charles H.Emerson, 2020**).

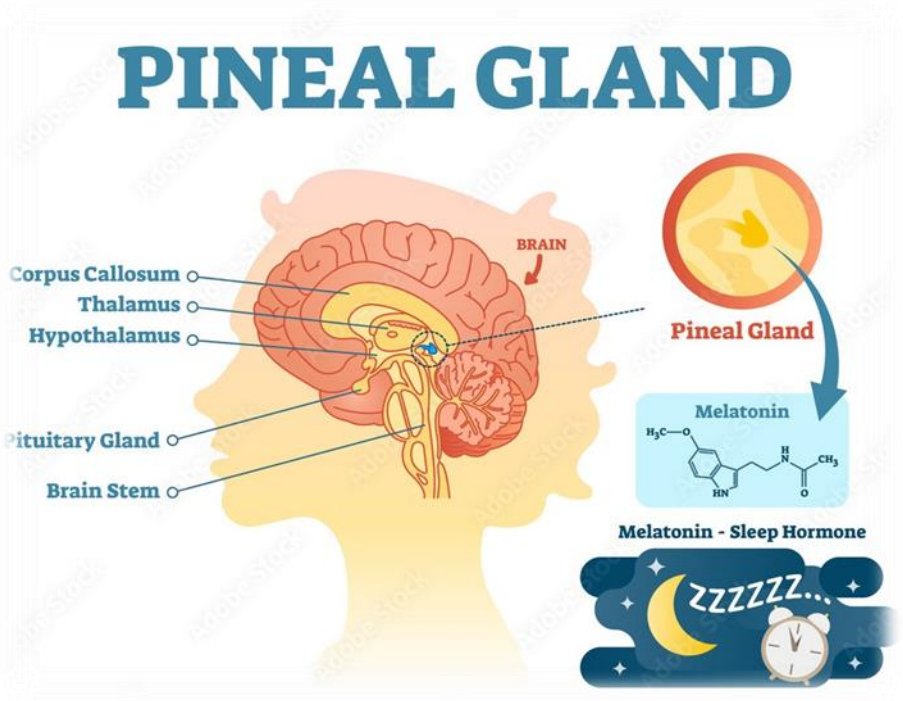

Figure 16: The location of the pineal gland in the human brain and the chemical structure of its main hormone, melatonin by **(Vector Mine stock. Adobe site)**

2-Pituitary gland

2-1 Definition

The pituitary gland is a major organ of the neuroendocrine glands, and it is small gland located inside a bony structure called (sella Turcica), this bony cavity is connected to the hypothalamus by the stalk of pituitary gland (**Marcel Maya ; Barry DPressman, 2011**), this gland arises from rathke's cyst, it is considered the main controller of the functionof most endocrine glands, which is why it is called the master gland, it also works under the control of the hypothalamus, which detects the levels of hormones produced by the glands that are under the control of the pituitary gland (Target glands) (**John D.Carmichael,2021**).

2-2 Anatomy and Function

The pituitary gland consists of two parts as follows: **(Suzan A. El Sayed et al., 2021)**

- Anterior lobe (adenohypaphysis): it constitutes 80% of the weight of the gland.
- Posterior lobe (neurohypophysis)

The pituitary gland regulates the production and secretion of peptide hormones that are important for the function of many glands (Adrenal gland, thyroid, etc.) (**Heather L Burrows, 1999**), each hormone is secreted by a specific type of cell, there is also a kind of integrative relationship between the pituitary gland and the hypothalamus, where there are some hormones

that are produced in the **hypothalamus**, but they are stored and released from the pituitary gland (Adrenocorticotropic hormone, antidiuretic hormone, oxytocin, etc.) (**John D.Carmichael, 2021**).

2-3 Pituitary Gland Hormones

Each lobe of the pituitary gland secretes its own hormones that have important roles within the body as follows:

●**Posterior lobe hormones (neurohypophysis) :(John D Carmichael, 2021):**

- **Antidiuretic** hormone (Vasopressin): a hormone that maintains the regulation of the amount of water excreted from kidneys and the balance of the amount of water in the body.
- **Oxytocin**: an important hormone, especially for women, as it prevents heavy bleeding at birth, because it causes the uterus to contract during and after childbirth to help prevent bleeding.

●**Anterior lobe (adenohypaphysis):** the anterior lobe produces six essential hormones :**(John D. Carmichael, 2021):**

1-Growth hormone: affects the shape and organization of the body, it is secreted by cells called somatotroph.

2-Thyroid stimulating hormone (**TSH**): stimulates the thyroid gland thyroxin (**T4**) and triiodothyronine (**T3**), TSH is secreted by cells called (Thyrotropes).

3-Prolactin: it stimulates the female mammary glands to produce milk; it is secreted by cells called lactotroph.

4-Reproductive hormones: these include follicle-stimulating hormone (**FSH**) and luteinizing hormone (**LH**).

5-Adrenocorticotropic hormone (**ACTH**): stimulates the adrenal gland to secrete hormone called cortisol.

6-Hormones with analgesic properties: like endorphin, and enkephalin.

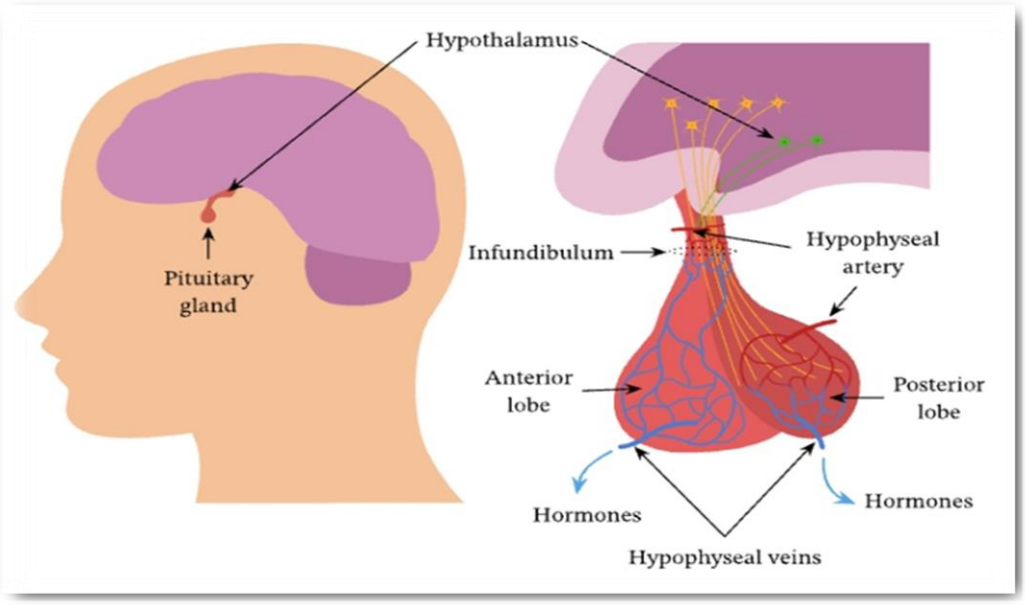

Figure 17: The location of pituitary gland in the human brain and its anatomical composition (**nagwa site**).

3-Posterior fossa

3-1 Definition

Posterior fossa, also known as posterior cranial fossa, the posterior fossa is the posterior basal side of the skull and houses both the brainstem and the cerebellum, it is the deepest fossil among the other fossils found in the cranial cavity (anterior cranial fossa and middle cranial fossa) (**Briony Adams, 2021**), the posterior fossa contains nerve pathways and arterioles, and it considered among the most anatomically complex structures within the skull (**Albert L.RhotonJr, 2015**).

3-2 Anatomical Structure

In terms of its anatomical structure, the posterior fossa consists of the temporal and occipital bones, as the following division bound it:

- **Anterior and middle**: The backbone of the sphenoid bone.
- **Anterior and side:** The upper part of the petrous part of the temporal bone.
- **Posteriorly:** It is bounded by the inner surface of the squamous part of the occipital bone.
- **The floor**: It consists of the squamous and condylar parts of the occipital bone, and the mastoid part of the temporal bone, (**Briony Adams, 2021**).

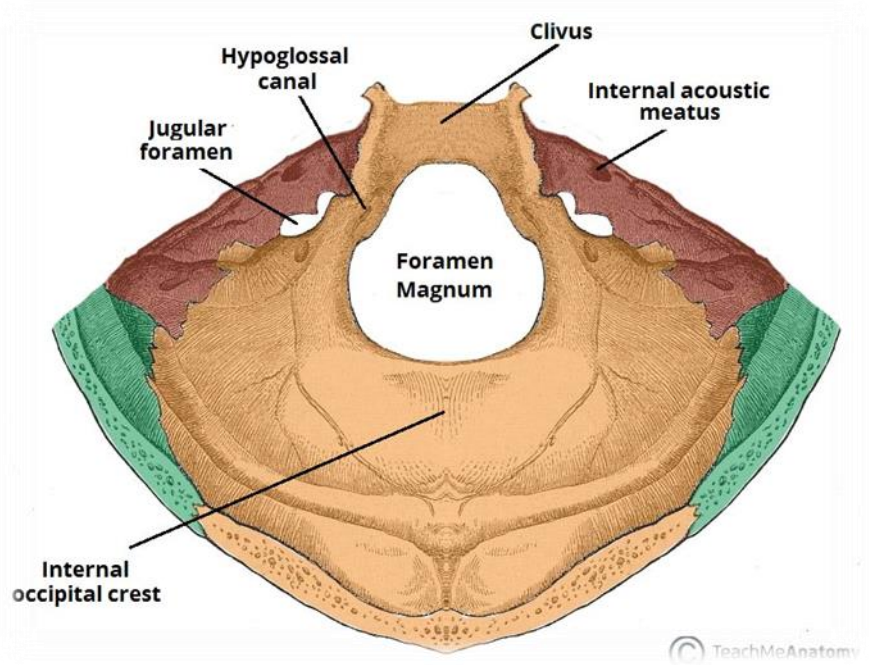

Figure 18: illustration of an anatomical section of the skull, showing in the drawing the posterior cranial fossa delimited by black lines (**Teach MeAnatomy site, Briony Adams, 2021**).

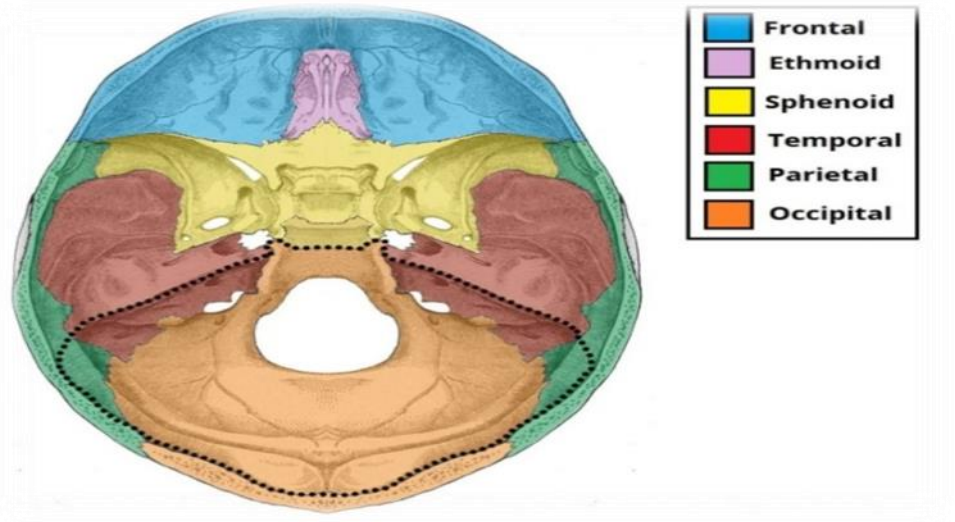

Figure 19: illustration showing bony formation of the posterior cranial fossa (**Teach me anatomy site, Briony Adams, 2021**)

4-Thalamus:

4-1 Thalamus Definition

The first discovery of the thalamus is attributed to Galen, who according to his ninth book, indicated that he had seen, according to his description, the geniculate nucleus, but he did not speak or hint directly that he saw the thalamus, a group of physicians indicated in **1968** when translating Galen's book (**De usu partium**) that what he had noticed in the bull's brain might be a choroidal fissure belonging to the descending part of the lateral ventricle (**Edwars G Jones, 2007**)

4-2 Anatomy & Function

- Anatomically the thalamus is a structure located centrally in the brain, which is a double structure or is a gray matter structure located above the midbrain, the thalamus consists of a large number of neurons "nuclei", numbering approximately **15** nuclei, which are the main components of the dorsal thalamus, among the main types of these nuclei, the most famous are: relay nuclei, association nuclei, midline nuclei, and retinal nuclei, the other part of the thalamus is called the ventral thalamus, which is the reticular thalamic nucleus (**S.Murray sherman et Rainer W Guillery,2006**)

- Basically, the thalamus is considered as a station for filtering information between the brain and the rest of the body, as it plays an important role as a sensory stage in the auditory, gustatory and visual systems, the thalamus also has roles in motor activity, memory, and others (**Hal Blumenfeld, 2002**)
- Functionally, the thalamus is divided into five main components, which are nuclei, these nuclei are made up of neurons, these nuclei may be of an inhibitory or excitatory nature (**Juan Jose Valenzuela-Fuenzalida *et al*., 2021**), it is divided as follows:

1-Sensory nuclei: it has an important role in regulating sensory fields, exept the sense of smell.

2-Retinal and internal nuclei: especially for regulating pain and agitation

3-Effector nuclei: that controls motor language function

4-Associative nuclei: relevant to cognitive functions

5-Limbic nuclei: especially for mood and motivation (**Juan Jose Valenzuela-Fuenzalida *et al.*, 2021**)

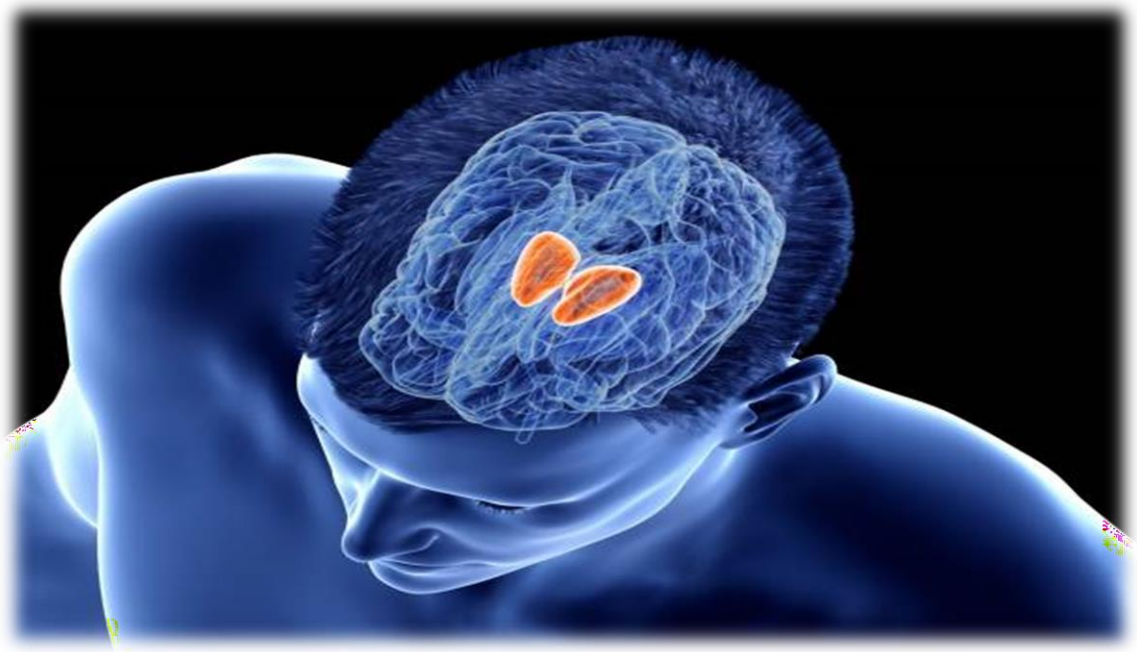

Figure 20:3D anatomical image of the thalamus, where it appears in the center of the brain in orange by **(Sebastian Kaulitzki geety images, site**)

5-Spinal cord

The spinal cord is a tubular bundle of tissues (of nervous nature) and supporting cells, it is considered the most important structure connecting the body and the brain, this unique structure extends from the brain stem to the lumbar vertebral (**Mike Bath, 2020**), its normal length is between **40** and **50** cm and its diameter is up to **1,5** cm, which is slightly longer in men (**Dr Çağrihan KiliÇ**), The brain and spinal cord together form the central nervous system, and the spinal cord is made of white and gray matter like the brain

The spinal cord's unique configuration of nerves enables it to transmit outgoing and incoming nerve messages through these nerves between the brain and the rest of the body, the spinal cord is also a center for reflexes (reflexes such as the knee jerk reflex) (**Steven A Goldman, 2018**)

5-1 The Spinal Cord Structure Organization

The spinal cord consists of three layers of tissue (meninges), as well as of spinal nerves, which are between the vertebrae that number **31** pairs, there are two branches (two roots) for each nerve:

- **In the front (anterior or kinetic root):** this carries commands from the brain and spinal cord to the rest of the body

- **In the back (sensory or posterior root):** this nerve transmits information from body parts to the brain (**Steven A Goldman, 2018**)

  - The layers of tissue that protect the spinal cord are called; arachnoid mater, pia mater, dura mater, these tissue layers also called the meninges, are arranged in order from outside to inside as follows (**Rachel Nall, 2019**):
  - **Dura Mater:** the outer protective layer of the spinal cord
  - **Epidural Space:** it is between the dura mater and the arachnoid space, it is where doctors insert a local anesthetic to relieve pain in some medical procedures
  - **Arachnoid Mater**: it is the middle tissue layer in the spinal cord
  - **Subarachnoid Space:** between the arachnoid mater and the pia mater, cerebrospinal fluid (**CSF**) is located in this space
  - **Pia Mater:** it is the layer that directly covers the spinal cord

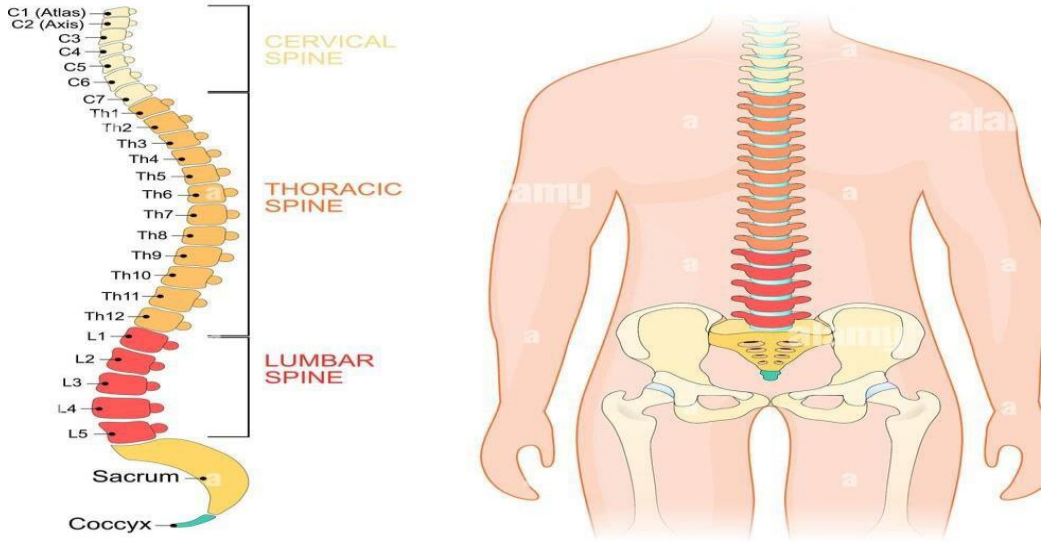

Figure 21: a picture showing the location of the spinal cord in the body and its parts (**Tetiana Zhabska, Alamy site, 2019**)

IV-Oxidative stress in neurodegenerative diseases

Free radicals are highly reactive molecules created through many biological processes such as the production of super-radicals and hydroxyl or the oxidation of catecholamines and activation of the electrons of the arachidonic acid product, they have the ability to combine with other molecules such as oxygen to form what is known as reactive oxygen species (ROS) **(Aiken CT *et al*).**

1-What is Oxidative stress?

Oxidative stress is a result of the body's inability to get rid of reactive oxygen species due to an imbalance between the production of reactive substances and antioxidants, which leads to an accumulation of ROS, which causes a change in cell functions or damage **(Ienco EC *et al.*, 2011).**

Oxidative stress is associated with the occurrence of many neurological diseases such as Alzheimer's disease, Parkinson's disease and many other degenerative diseases because reactive oxygen species target several important centers in neurons such as ADN and ARN by affecting the bases of pyridine and purine, which leads to mutations in Copying the DNA, which inevitably leads to a defect in the peptide chain of proteins, and consequently, a defect in the structure of the proteins and their function**(W. Droge,2002)**

2-Evidence of oxidative stress in neurodegenerative diseases:

Neuronal oxidation includes oxidation of proteins, lipids and DNA **(Adibhatla RM et Hatcher JF, 2010) (Bochkov VN et al., 2010) (Sedelnikova OA et al., 2010)**, where unsaturated lipids are oxidized due to the attack of free radicals to form lipid peroxide, as the repetition of this process leads to the formation of products such as F2-isoprostanes and 4-hydroxy-2, 3-nonenal (HNE), which inhibits neurotransmitters such as glutamate and neurotransmitters, and activates kinases, which leads to apoptosis **(Keller JN et al., 1997) (Tamagno E et al., 2003).**

Proteins are affected by reactive species that cause their oxidation and turn into inhibitors of proteasome activity that fight oxidized proteins **(Jung T et al., 2009)**, which leads to the accumulation of abnormal proteins, which leads to the phenomenon of necrosis in cells and neurodegenerative diseases **(Ciechanover A et Brundin P, 2003) (Dahlmann B, 2007).**

Metal ions play a key role in regulating biological processes inside the brain, such as oxidation and restoration, but their effectiveness is affected by free radicals **(Barnham KJ et Bush Al, 2008)**, where an exchange of electrons occurs between them, which leads to an imbalance in ions such as Cu2 + or Fe3 +, which causes an imbalance in the sequence of brain signals, which has been proven to be It is related to neurological diseases such as Parkinson's and Alzheimer's **(Ke Y et Qian ZM, 2007) (Zecca L et al., 2004) (Salvador GA et al., 2010).**

Parkinson's disease is the second most common neurological disease **(Wakabayashi K et al., 2007)** Studies have shown that there are signs of oxidative stress in people with this disease in lipids and proteins within brain tissue **(Chu Y et al., 2009)**, where it affects dopamine through free radicals, which causes a mutation on a protein called α-synuclein, which is known for its role in regulating dopamine in the brain. This impairs the storage of dopamine inside the vesicles and accumulates deposits of oxidized proteins **(Lotharius J et Brundin P, 2002).**

Oxidative stress enhances the risk of Alzheimer's disease **(Querfurth HW et LaFerla FM, 2010)**, as it has been found that oxidative effects within brain tissues such as oxidized proteins, impaired proteasome activity **(Poppek D et al., 2006) (Keck S et al., 2003)**, increased DNA oxidation in mitochondria and nuclei **(Pratico D, 2008)**, as well as iron oxidation and aging plaques rich in Aβ protein, increase the ability of Aβ protein to bind to selective metals such as Zinc and iron, which are oxidized through metal ions **(Atwood CS et al., 1998) (Atwood CS et al., 2000).**

3-The Antioxidant System:

It is a group of antioxidant enzymes and small molecule antioxidants that control the cellular levels of ROS **(L. Miao et D.K.S. Clair, 2009).**

3-1-Superoxide Dismutase:

It is one of the most important antioxidant enzymes, as the superoxide dismutase (SODs) family works to remove the super anion radicals coming from outside the cell with those that arise inside the mitochondria as by-products of oxygen metabolism **(L. Miao et D.K.S. Clair, 2009).**

There are **3** types of SODs in mammals which are copper oxide superoxide dismutase and zinc superoxide dismutase, manganese superoxide dismutase, extracellular superoxide dismutase **(L. Miao et D.K.S. Clair, 2009).**

Although these enzymes are similar in function, they differ in terms of their protein structure properties, and chromosome localization **(L. Miao et D.K.S. Clair, 2009).**

3-2 glutathione peroxidase:

A group of multiple isozymes that catalyze the reduction of H2O2 or organic hydroperoxides to water or alcohols using reduced glutathione **(R. Margis et al., 2008).**

There are four main types of glutathione peroxidase in mammalian tissues that are more localized in glial cells, where their activity is higher than in neurons **(R. Margis et al., 2008).**

3-3 Catalase:

A ferriheme-containing enzyme that converts hydrogen peroxide into water **(W. Dröge, 2002)**, it is found in peroxisomes and has an important role at high levels of hydrogen peroxide production **(W. Dröge, 2002)**.

3-4 Non-enzymatic Antioxidants:

3-4-1 GSH:

GSH is the main antioxidant in the central nervous system with the ability to act non-enzymatically directly with free radicals **(R. Dringen et J. Hirrlinger, 2003)**, in particular, hydroxyl radicals, and nitric oxide, Superoxide radicals, carbon radicals to remove them also can work enzymatically to remove H2O2 and keep GSH in a reduced state **(R. Dringen et J. Hirrlinger, 2003).**

3-4-2Vitamin E:

Vitamin E protects and reduces the effect of peroxide on the lipids in the membranes of the central nervous system because it has antioxidant properties **(V. Conte et al., 2004).**

IV – Nervous Breakdown

1-Definition of nervous breakdown

A nervous breakdown is a term used to describe a state of distress, mental disorder, or illness that occurs to a person suddenly as a result of accumulation and stress, this term first appeared

in medical treatise by physicians in **1901** (**Jerry useem, 2021**), however, nervous breakdown can not be considered a medical term nor does it refer to a specific mantal illness, but this does not mean that nervous breakdown is a normal response (**Daniel K Hall Flavin, MD**)

The term has been used to refer to a range of mental health conditions such as depression, acute stress disorder and anxiety

2- Symptoms of nervous breakdown

Its symptoms were classified into physical, psychological and behavioral symptoms, among these purposes are the following (**Annamarya Scaccia,2021**) :

a.**Symptoms of depression:** it includes feelings of guilt and constant sadness, social withdrawal, thoughts of suicide, loss of interest in life, interest in hobbies, ect

b. **Anxiety symptoms:** the main symptoms of it are malaise, muscle tension and sweating

c. **Insomnia symptoms:** like difficulty sleeping

d. **Symptoms of post-traumatic stress disorder:** because of a trauma or an accident that happened to the person, and he became afraid of the same incident being repeated with him

e. **Panic Attacks**

3-Causes of nervous breakdown

A person reaches a nervous breakdown when the external or internal psychological influences exceed the limits that he can bear, some of the causes of this stress or collapse (**Webmd,site, Medically reviewed by; Dan Brennan,2020**)

- Problems or pressures at work, family, school, ect
- Financial problems such as losing a job or not paying a loan
- Change in emotional relationships
- A big and shocking event like the death of a close person
- A personal or family history of mental disorders or anxiety may be a risk factor for a nervous breakdown

4-Various forms of nervous breakdown

Doctors divide nervous breakdown into three main types (**Altibbi,Site**):

- **First type**: it is related to the person's hidden and negative feeling inside him, and the person feels helpless in the face of life's pressures
- **Second type:** this type is a severe type because it is represented in the person being exposed to severe and many problems that affect his subconscious mind, as the person becomes very tense and gets angry at any problem he faces, even if it is small
- **Third type**: especially for sensitive people who can not stand the pressures they are exposed to

5-Diagnosis of nervous breakdown

There is no specific diagnosis or ways to know that a person will have a nervous breakdown, but there are signs of a nervous breakdown such as stress, which can become a source of anxiety, panic attacks, as well as collapse can be a sign of a mental health condition, therefore, the most appropriate solution is to go to a doctor as soon as cases of collapse appear, the doctor may help you in treating the physical symptoms, or they may advise you to see a doctor or psychologist to treat you psychologically (**Jennifer Huizen, 2020**)

6-Treatments for nervous breakdown

The type of treatment depends on the diagnosis, so the first step you should take is:

- Go to a doctor or psychologist
- **Talke therapy:** it is included in psychotherapy, which is an effective treatment in many cases, one of the most popular types of psychotherapy is cognitive behavioral therapy (**CBT**), which is effective in treating anxiety and depression
- You can also take medications as prescribed by the doctor, such as antidepressants and even antipsychotics in some cases
- **Lifestyle change:** such as getting enough sleep and avoiding staying up late, eating a healthy diet, exercising, finding new hobbies, avoiding alcohol and caffeine (**Annamarya Scaccia, 2021**)

7-Antidepressant treatment

Antidepressants are used to control many mental and neurological diseases and depressive states.

These drugs work to balance certain types of natural chemical compounds found in the brain known as neurotransmitters.

1-Definition of antidepressant drugs

Antidepressants are drugs that help relieve symptoms of depression and improve the patient's mood by adjusting the proportion of chemicals in the brain and returning it to its normal state **(Courtet, P., & Lopez-Castroman, J, 2017).**

The types of antidepressants vary depending on the type of disease, how effective the medication is, and the patient's response **(Courtet, P., & Lopez-Castroman, J, 2017)**

Antidepressants can cause side effects and may lead to suicide **(Satish Valluri *et al.*, 2010)**

2-Classification of antidepressant drugs

Antidepressants are classified according to three criteria:

Chemical Structure, Biochemical Actions, Spectrum of Activity (Potential) **(Fasipe, O, 2018).**

2-1-Monoamine Oxidase Inhibitors (MAOIs)

Monoamine oxidase inhibitors are very effective in treating depression-related diseases. They are prescribed with a special diet because they have side effects that can cause health risks (**Nathan Herrmann and Scott E. Walker, 2013).**

Monoamine oxidase inhibitors affect neurotransmitters in the brain to change the chemical elements of areas that are associated with depression **(Tobe EH, 2014)**

Where the enzyme monoamine oxidase removes the neurotransmitters inside the brain dopamine, norepinephrine and serotonin, which increases the presence of chemical elements as it facilitates the process of affecting the cells affected by depression **(Tobe EH, 2014)**

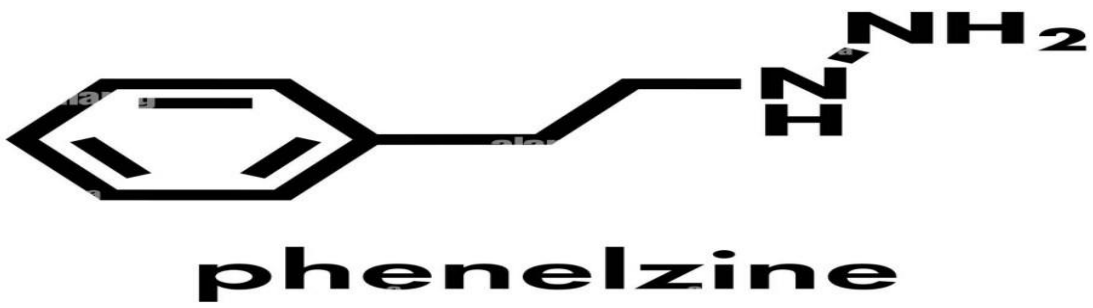

Figure 22: MAOIs antidepressant drugs structure phenelzine **(alamy site, 2018)**

2-2-Tricyclic antidepressants (TCAs)

Tricyclic antidepressants are a group of medicines that appeared in the past and were used to treat depression by increasing both serotonin and norepinephrine, but later this type of medicine was abandoned because it has significant side effects such as lowering blood pressure and difficulty urinating **(Gabriel M *et al.*, 2017).**

Tricyclic antidepressants block the uptake of neurotransmitters (serotonin and norepinephrine), which increases their levels in the brain, making the affected areas relax and adjusting mood **(Hirsch M, *et al.*, 2019).**

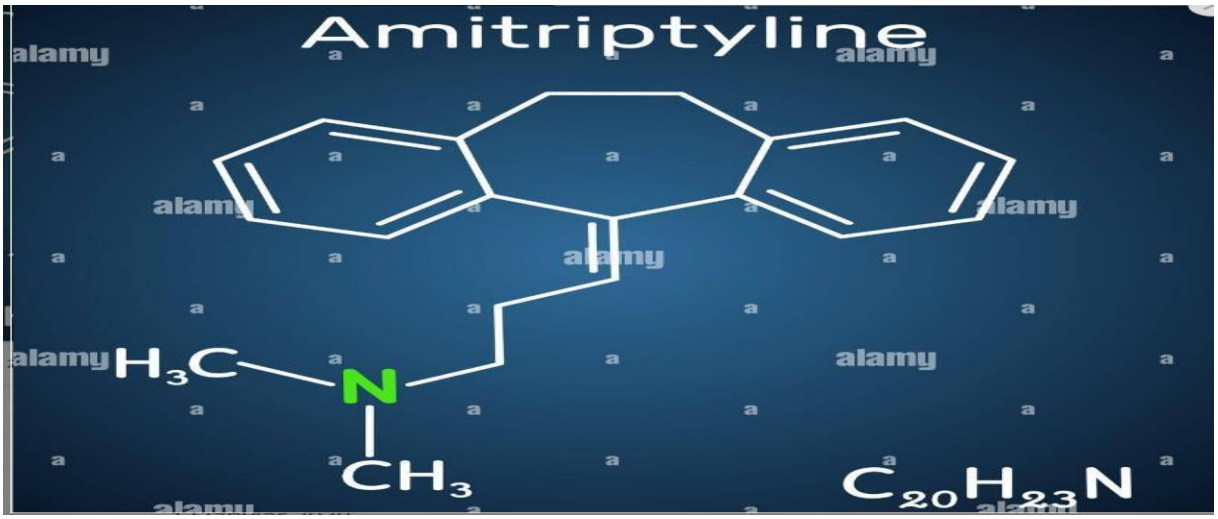

Figure 22: Tricyclic antidepressant drugs structure Amitriptyline (**netdoctor site, 2010)**

2-3-Specific Serotonin Reuptake Inhibitors (SSRIs)

SSRIs are the most common type of antidepressant used to treat the most severe effects of depression, and they rarely show side effects **(Moja PL, 2005).**

Selective serotonin reuptake inhibitors (SSRIs) affect by increasing the presence of the neurotransmitter serotonin by stopping the process of its uptake in the synapse, which increases its percentage, improving the passage of nerve impulses and affecting sensitive areas in the brain **(Lexapro,2019).**

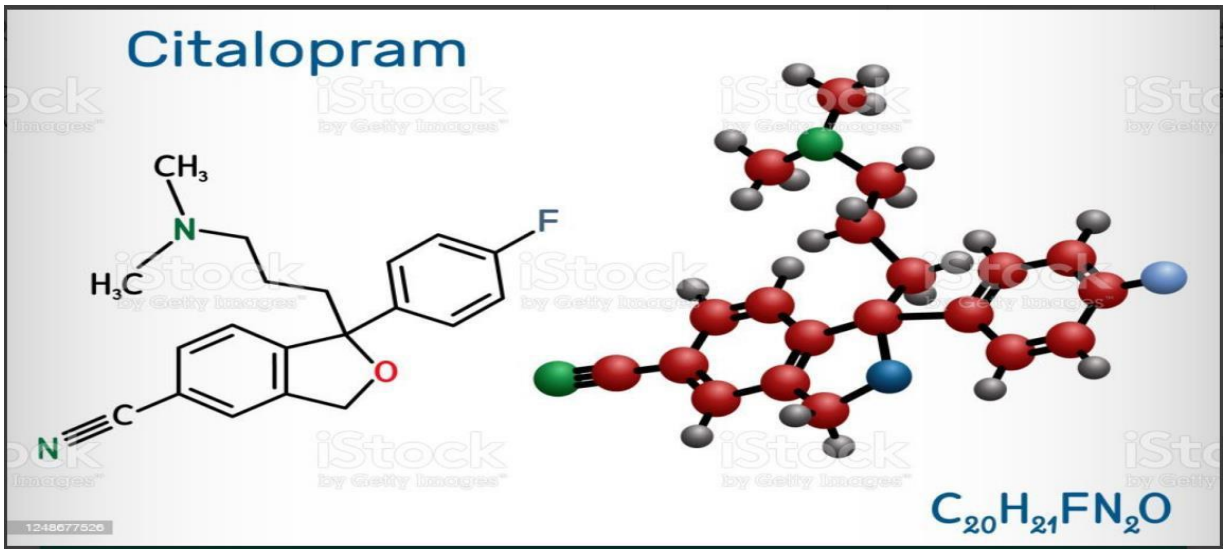

Figure 23 : SSRIs antidepressant drugs **(pharmaonline site,2014)**

2-4-Other antidepressants

Other antidepressants differ from the previous classes and have many different chemical formulas, such as maprotiline, mianserin, mirtazapine, tianeptine, which are derivatives of dibenzothiazepine that block the reuptake of serotonin and norepinephrine **(Lopez Castroman, 2017).**

3-Toxicokinetics of Antidepressant Drugs

Like all drugs, antidepressants go through several stages within the organism, or what is known as toxicokinetics absorption, distribution, metabolism and elimination (**Preskorn S, 1982).**

3-1-Absorption of antidepressants

Antidepressants are often absorbed orally, except in some severe cases (intramuscular or intravenous injection) **(Harmer CJ *et al.*, 2017).**

Some studies have also shown that absorption through the digestive system is relatively slow, due to the weakness of the ionic bases inside the stomach and their anti-choline effect, which slows down the absorption process **(Harmer CJ *et al.*, 2017).**

3-2-Distribution of antidepressants

After the antidepressant enters the body through one of the absorption pathways, it crosses into the bloodstream, where its molecules interact with various proteins and lipids in the bloodstream **(Hébert *et al.*, 2008).**

Tricyclic antidepressants also have a high tissue affinity, and this may affect the process of distribution within tissues, as the antidepressant begins to give effect gradually during this process **(Hébert *et al.*, 2008).**

3-3- Metabolism of antidepressants

Metabolism occurs mainly in the liver, the goal of this stage is to make the antidepressant more hydrophilic by making chemicals modifications on it, and this process affects its percentage in the body, where:

-Oxidation and hydroxylation of the nucleus of imipramine on the C2 or C10 carbon by cytochrome P450 and progressive side chain degradation and N-demethylation, and N-oxidation. At the end of the reactions an active desipramine is produced, which will subsequently undergo the enterohepatic cycle (EHC) **(Gardiner SJ, Begg EJ, 2006)**

In the second phase: Glucuronidation of hydroxylated metabolites **(Noro Psikiyatr, 2017).**

3-4-Elimination of antidepressants

The metabolic derivatives eliminated by the bile are led to join the enterohepatic circulation because they have a very high affinity for the tissues **(Ghaemi, S *et al.*, 2001).**

Antidepressants have a long half-life, which makes their elimination long-term, as it may take a day or two **(Baldessarini, 2001).**

4-Indications of antidepressant drugs

Antidepressants have several different types that differ according to their composition, effect, and goals of use, and this is done by evaluating the patient's condition and the extent of his response to treatment **(Simon, G.E, 2002)**

Most antidepressants have shown great effectiveness in treating several mental and organic diseases, or at least alleviating their severity, these are most of the conditions for which antidepressants can be used as treatment:

- Obsessive compulsive disorder (OCD) **(Simon, G.E, 2002)**

- Moderate and severe depression and its prevention **(FreemantleN *et al.*, 2000)**

-Generalized anxiety disorder **(Simon, G.E, 2002)**

- Severe anxiety states **(Ritter J, 2020)**

-Post-traumatic stress disorder **(FreemantleN *et al.*, 2000)**

- Childhood enuresis **(Preskorn SH, 2019)**

- Severe migraine **(Ritter J, 2020)**

-Neuropathy diseases **(Preskorn SH, 2019)**

5- Mechanisms of action of antidepressant drugs

- Antidepressants modify the chemical imbalances of neurotransmitters that are located in the vesicles of nerve cells in the brain, which directly affects behavior and mood primarily **(Müller HJ *et al.*, 1995).**
- The outer end of a nerve releases neurotransmitters such as dopamine, norepinephrine, or serotonin in what is known as the recovery phenomenon **(Bleakley S *et al.*, 2011).**
- Monoamine oxidase inhibitors block the absorption of one of these neurotransmitters, serotonin, through special selective receptors that inhibit the work of the enzymes responsible for its degradation, the most important of which is the enzyme monoamine oxidase A, which increases its concentration in the brain **(Baker GB *et al.*, 1992).**
- Tricyclic antidepressants boost neurotransmitters called norepinephrine, which are low in severe depression by inhibiting the enzymes that uptake it, which reduces depression and improves sleep quality **(Müller HJ *et al.*, 1995).**

This table represents some types of antidepressants and their mechanism of action:

Table 04: Antidepressants and their mechanism of action **(Anders Wessling, joakin Ramsberg,2008)**

Name of antidepressant	Pharmaceutical Name	mechanism of action
Amitriptyline	Saroten	Serotonin-norepinephrine reuptake inhibitors
Moclobemide	Aurorix- roche + generics	MAO inhibitor
Maprotiline	Ludiomil- Novartis	norepinephrine reuptake inhibitors
Fluoxetine	Fontex	Serotonin Reuptake inhibitors
Paroxetine	Seroxat- glaxosk + generics	Serotonin Reuptake inhibitors
Sertraline	Zoloft-Pfizer + generics	Serotonin Reuptake inhibitors
Fluvoxamine	Fevarin-solvaypharma	Serotonin Reuptake inhibitors

6-The effectiveness of antidepressants

To ensure the effectiveness of the antidepressant, the results should be measured before and after treatment, where information is taken about the condition of the patient or the volunteer before using the drug and compared with the results obtained after 8 weeks from the start date because antidepressants require at least 3 weeks for their effects to appear**. (Simon, G.E, 2002).**

- Most studies have agreed that antidepressants have the same clinical efficacy after comparing these drugs with each other. An experiment was conducted in which researchers compared the effectiveness of 12 different types of antidepressants. The results showed that there was no significant difference in effectiveness between milnacipran and bupropion and other drugs except reboxetine which was less effective **(Zarifian, 1996).**
- 522 international studies conducted using 21 different types of antidepressants showed that 120 thousand patients responded to treatment with different types of these drugs with great effectiveness and can help a lot for the final treatment **(Zarifian, 1996).**
- But although there are more than 300 million people suffering from diseases such as depression and anxiety, but only 1/6 of them use antidepressants as the main treatment despite the effective results that have been proven on them, and this may be due to the fear of their negative side effects (**FreemantleN *et al.*,2000).**

These studies give us a clear picture of the effectiveness of antidepressants, and at the present time, more in-depth studies are being conducted to find out the differences between the drugs among them, despite their limitations (**Maël Lemoine, 2022).**

7-Adverse effects with antidepressants

Like most drugs, antidepressants have side effects that vary in severity depending on the amount and effect of this drug on the organism where a doctor should be consulted in very serious cases, and these are the most important effects that have appeared in people who use antidepressants permanently (**David Healy, 2006).**

- Severe Nausea and Diarrhea **(Carvalho LA *et al.*, 2009).**
- Headache, Dizziness and Insomnia (**David Healy, 2006).**
- Serotonin syndrome: It appears in people who use serotonin inhibitor, the most prominent effects of which are high fever, convulsions and irregular heartbeat. (**Healy, D., & Whitaker, C, 2003).**
- Eye disorders (Pain, Redness, Pupil Disturbances) **(Khan A *et al.*, 2000)**
- Mania, Psychosis, Or Confusion **(Khan A *et al.*, 2000)**

These effects can be permanent in some cases or appear at the end of treatment (**David Healy, 2006).**

Chapter 3:

Aspects of phytotherapy neurodegenerative diseases

A-Neuroprotective phytochemicals and their mode of action on neurodegenerative disorders:

-Effect of phytochemicals in memory, cognition and Alzheimer's disease:

I-I-Alzheimer

Alzheimer's disease is one of the most well-known diseases among the people, where it is known that it is a disease that affects older people and leads to poor memory, but there are many things are unknown about the real reasons or whether it has an effective treatment

1-Definition of Alzheimer

The origin of the name goes back to **1907**, to the German psychiatrist **Alois Alzheimer**, and this is according to his description of the case of a **51**-year-old woman who was suffering from a rapid deterioration in her memory and some other mental disorders **(Rudy J Castellani *et al*., 2010)**

It was defined as a neurodegenerative disorder that gradually spreads and causes death, starting with an initial impairment of memory, up to a complete loss of perception, reasoning and memory (**William R. Markesbery,1998**), it affects especially individuals over the age of **65**, and leads to behavioral changes and leads to the accumulation of deposits of amyloid beta (**β**) and tau in the brain, the brain of Alzheimer's patient suffers from the loss of neurons in the brain and the formation of neurofibrillary tangles (**Liana G Apostolova**, **2016**)

2-Symptoms of Alzheimer

Alzheimer's disease is a progressive disease, meaning that symptoms get worse over time, and it causes almost the same symptoms as other types of dementia, such as memory impairment, except that it differs from dementia in other things, including that it affects recent memory more than other mental functions (**Juebin Huang, 2021**)

We mention some of the symptoms that appear and characterize people with Alzheimer's disease: (**Markus Mac Gill, 2020**)

- The well-known symptom, which tends to be one of the first symptoms that appears, is memory loss so that it is gradual as the patient finds is difficult to remember new information and loses things and forgets places

- ❖ symptoms of recognition problems: the patient becomes less able to remember faces and details and use the tools we use in our daily lives such as turning on the air conditioner, using eating spoons and others
- ❖ problems with spatial perception: the patient has difficulty walking and stumbles a lot and things fall from his hands
- ❖ difficulty thinking, forgetting words, making many linguistic errors in speech and asking the same questions
- ❖ behavioral changes such as feeling angry and aggressive

3-Causes of Alzheimer

The researchers do not know the main reason that the primary causes of Alzheimer's disease, but there are beliefs that the disease is caused by two types of defects, or vice versa, that these defects occur due to Alzheimer's disease, where they are represented in: (**Arefa Cassoobhoy, 2020**)

- ❖ neurofibrillary tangle: these twisted fibers inside brain cells prevent nutrients from moving from one part of the cell to another
- ❖ beta amyloid plaques: they are sticky clumps of protein that accumulate between neurons in the brain of an Alzheimer's patient, while they are disintegrating in healthy brains So, Beta plaques and tangles cause cell damage, resulting in changes such as memory loss, but scientists do not know exactly when these tangles and this plaque clump begin in cells, and cells produce less amounts of the neurotransmitter **(acetyl choline)**
- ❖ 2/genetic factors play a role in the occurrence of Alzheimer's with about **5%** to **15%** of cases occurring in families (**Juebin Huang, 2021**)

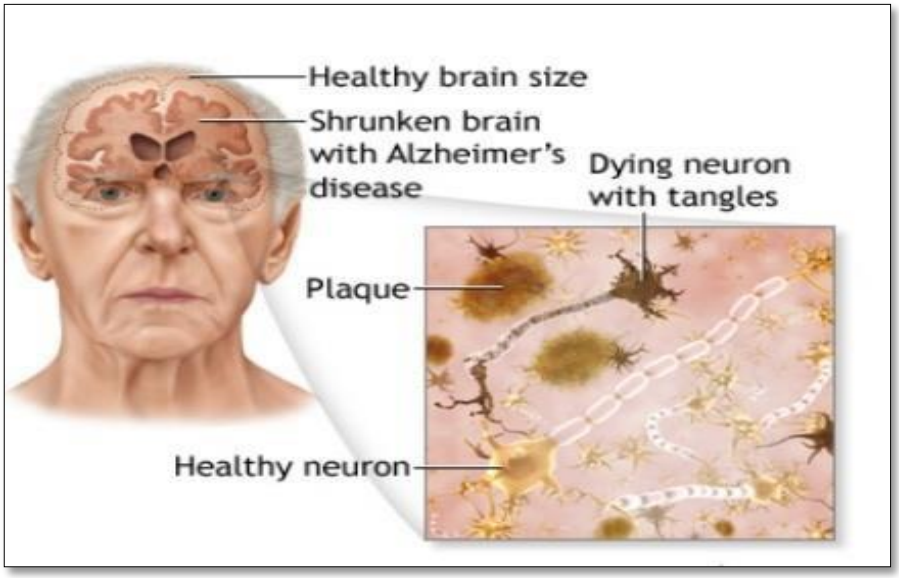

Figure 24: illustrative image of the shrunken brain of an Alzheimer's patient and the shape of neurons in the brain of an Alzheimer's patient compared to the normal brain (**Gray Caffe**)

4-Diagnostic of Alzheimer

Easy for doctors to diagnose Alzheimer's disease by knowing and distinguishing Alzheimer's disease from other causes of memory loss, there is no single test, if the doctor suspected the existence of the disease, he asks questions for the person or his family, he may also perform the following tests: (**Markus Mac Grill, 2020**)

- Memory and cognitive abilities test: to assess how well a person thinks and remembers
- Mental and neurological function test: to balance, reflexes and senses
- Blood or urine tests, as well as some tests such as computerized tomography (**CT**) scans and magnetic resonance imaging (**MRI**), this is to rule out other causes as the diagnosis of Alzheimer's disease is usually similar to the diagnosis of other types of dementia (**Juebin Huang, 2021**)

5- The effect of Alzheimer's disease on the brain

One of the most prominent effects of Alzheimer's disease on the person affected is the shrinkage of the brain so that the appearance of the brain of the person with Alzheimer's disease is different from the normal person, among the effects and changes that can be observed on the

brain using magnetic resonance imaging (**MRI**) are the following effects: (**Christine Kennard, 2022**)

- Cerebral cortex atrophy
- Decreased amount of brain matter in the folds of the brain
- Enlargement of spaces in the folds of the brain
- Microscopic traces found in the brain of an Alzheimer's patient: it can only be observed by taking samples of brain tissue, which is taken after autopsy, where we find in the affected brain two distinct things; neurofibrillary tangles and amyloid plaques outside neurons and neurofibrillary tangles inside neurons
- Loss of neurons in grey and white matter, which leads to tissue atrophy (**Norbert Schuff *et al*., 1998**)

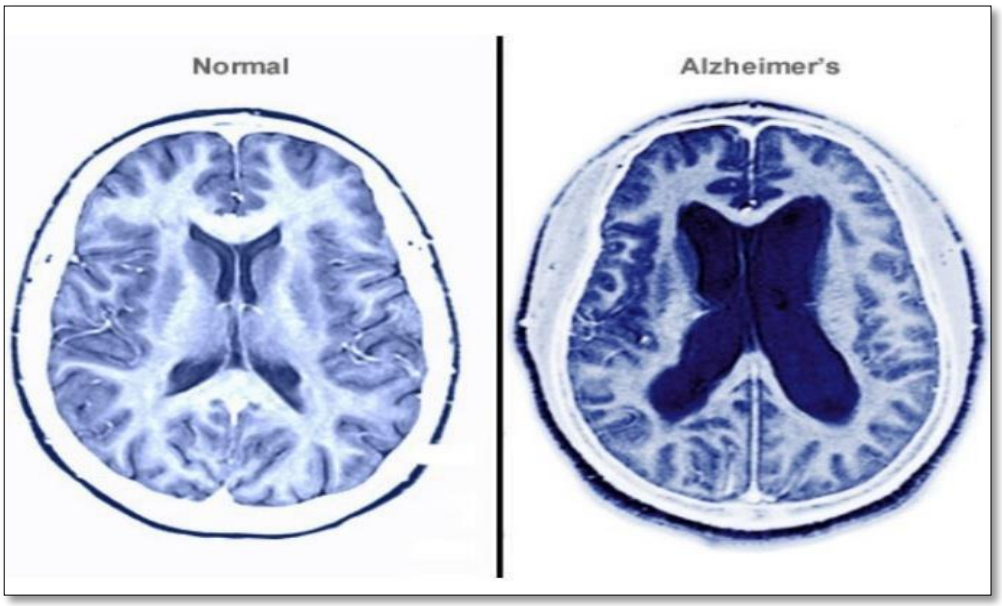

Figure 25: illustrative image of a brain CT scan showing the difference between the normal brain and the brain of an Alzheimer's patient (**Gray Caffe**)

6-Alzheimer's disease prevention

There are no effective measures, but it is believed that factors specific to a healthy lifestyle have a role in reducing the risk of Alzheimer's, some tips that promote a person's overall healthy: (**Jonathan Graff Radford, 2022**)

-A balanced and healthy diet

-Avoid smoking

-Physical activity

-Taking care of mental health by reading and using memory skills

7-Treatments against Alzheimer

There is no main and effective treatment for Alzheimer's disease, as it is known that we cannot reverse the death of brain cells, but treatment of symptoms and alleviation of its effects is available (**Markus Mac Gill, 2020**), some of the measures and treatments for Alzheimer's symptoms (**Liana G Apostolova, 2016**):

- The first treatment measures for behavioral symptoms are non-pharmacological, such as providing safety measures, a clam and familiar environment, adequate lighting, and dealing with aggressive behavior in positive language, as well as treating symptoms of depression with selective serotonin reuptake inhibitors (**SSRIS**)
- There are two types of medications to treat Alzheimer's disease symptoms that have been approved by the US food and drug administration (**FDA**): (**Anil Kumar et al., 2021**)
- Cholinesterase inhibitors: there are **3** drugs in this category, donepezil, rivastigmine, and galantamine
- Molecular antagonists of N-methyl D-aspartate (**NMDA**)
- Researchers are studying the possibility of moving towards and adopting phytochemicals as promising therapeutic agents (**Edwin L Cooper et Melissa J Ma, 2017**)

In 2021, the U.S.Food and Drug Administration (**FDA**) approved a new Alzheimer's disease drug called Aducanumb and his business name IS Aduhelm, it is used and effective only in patients who are in the beginning of Alzheimer's disease or who have mild cognitive impairment but his side effects have not been proven yet, this drug is an antibody that works to bind to the amyloid molecule that causes plaques in the brain, as the goal of the antibody in this drug is to stimulate the immune system when attached to plaques, where the body considers it a strange molecule on the organism and removes it with amyloid plaques (**Andrew E. Budsom, 2021**)

8- The role of phytotherapy against Alzheimer's disease

Over the past years, all efforts to treat Alzheimer's have failed and even medications have side effects and are ineffective, so herbal medicine is seen as an alternative to alleviating Alzheimer's disorders, since there are herbs that have been shown to have the ability to improve brain function this is due to their chemicals where there are plants containing antioxidants such as Flavonoids and Vitamin C, and E where these substances reduce the pathological physiological symptoms of neurodegeneration (**Ogbodo Onyebuchi John *et al*., 2021**)

A few herbal medicines have been clinically tested and some have shown effective functions against Alzheimer's such as: (**Ogbodo Onyebuchi John *et al*., 2021**)

- **Ginseng**: Studies have shown that the molecular enzymes found in this plant called ginsenosides have acetylcholinesterase (**AchE**) inhibitory actives.
- **Phyllanthus acidus**: Its plant extract is used to treat Alzheimer's symptoms because it increases the level of brain enzymes, and has antioxidant properties that improve cognitive function, reduce oxidative stress and also reduce lipid peroxide activity and Ache
- **Ginkgo biloba**: Used against cognitive impairment its plant extract contains glycosides, Flavones and lactones

8-1 The effect of active substance on slowing the progression of Alzheimer's disease

The effect of certain active substances on Alzheimer's disease:

- **Alkaloids**: (**Ya Pong Ng *et al*., 2015**)

- Alkaloids are important compounds that have long been an important source of treatment for brain disorders, so that two cholinesterase inhibitors approved by the American food and drug administration (**FDA**) for Alzheimer's disease Galantamine and Rivastigmine they are alkaloids

- There are other clinical trials have been conducted by other alkaloids such as caffeine, hyperzine A, but it hasn't proven convincingly effective against Alzheimer's

- **Flavonoids:** (**Katriona L. Hole et Robert J Williams, 2021**)
  - Flavonoids can reduce cognitive decline, studies also suggest that they can act as acetylcholinesterase (**AchE**) inhibitors (**Cristina Airoldi *et al*., 2018**)
- **Phenolic Compounds: (Tsuyoshi Hamaguchi *et al*., 2009)**

During experiments that proved that phenolic compounds have anti-accumulation effects of beta-amyloid, where they were tested on genetically modified mice that were fed phenolic compounds including Ferulic acid and Curcumin, the results showed that phenolic compounds may prevent the development of Alzheimer's disease by affecting the pathways of beta-amyloid accumulation

9-The role of aromatherapy against Alzheimer's disease

In recent years, there has been an increasing interest in non-pharmacological treatments for the treatment of irritability and aggression that appear on Alzheimer's patients, therefore, there is an increasing interest in aromatherapy in order to control Alzheimer's symptoms such as psychosis, aggression, and others (**Damiana Scuteri *et al*,2017**)

Aromatherapy may also have possibilities to improve cognitive function in Alzheimer's patients, as this type of treatment uses essential oils extracted from different parts of aromatic plants and used by inhalation or application topical or massage (**Aniruddha Banerjee *et al.*, 2021**)

In a study in which rosemary and lemon essential oils were used in the morning and orange and lavender in the evening on 28 elderly people suffering from dementia, **17** of them suffer from Alzheimer, the results of the study showed potential for improving cognitive functions as well as the absence of side effects, where the principle of action of aromatherapy through inhalation is through the aroma molecule that passes along the nasal cavity and adheres to the olfactory epithelium, where the stimulus is transmitted to the limbic system of the brain and the amygdala through the olfactory nerve system (**Daiki Jimbo *et al.*, 2009**)

9-1-The effect of essential oils on slowing the progression of Alzheimer's disease

Over the years, essential oils have had the importance and therapeutic potential of the mind thanks to the aroma molecules, as well as these oils do not lose their effect or wasted with time (**Aniruddha Banerjee *et al.*, 2021**), many essential oils are among the most aromatic treatments for dementia, such as Melissa (lemon balm) and lavender, where a study has proven the effectiveness of lemon balm and that it has positive effects on cognition (**Damiana Scuteri *et al.*, 2017**)

You should know that essential oils help improve symptoms such as insomnia and anxiety, but they are not considered a medical treatment, and their side effects are almost non-

existent for example, when an essential oil is inhaled, it stimulates olfactory receptors, which transmit positive or negative messages through the central nervous system to the limbic system (**Becky Upham, 2020**)

Some results emerged related to the role of essential oils in promoting neurotransmission by inhibiting acetyl cholinesterase and increasing acetylcholine in the degeneration of cholinergic neurons, thus essential oils may at least have the ability to reduce certain symptoms of Alzheimer's and mitigate its effects (**Aniruddha Banerjee *et al.*, 2021**)

9-1-1-Bergamot

Bergamot or (Citrus Bergamia) a rare type of citrus that is grown in Italy, especially in the south, where the Calabria region alone produces **90%** of the global crop (**Corey Whelan, 2018**)

The refreshing bergamot essential oil is used in aromatherapy and is used to reduce anxiety symptoms in nervous and depressed people (**Giacinto Bagetta *et al.*, 2010**)

Bergamot may also be used in the laboratory production of fruit juice, in study, when adding **10%** to **20%** bergamot juice to apple and apricot juice instead of artificial additives, the results were that apricot and apple juice fortified with bergamot juice showed an increase in its antioxidant properties and a decrease in ascorbic acid thus ensuring a product rich in antioxidants (**Rita Pernice *et al.*, 2009**)

9-1-2-Ginger

Ginger or (Zingiber officinal) it is a perennial tropical herbaceous plant that reaches a foot tall with grass leaves, it is known as one of the most widely used herbal supplements and is widely used for culinary purposes, it is a member of the family of plants that includes cardamom and turmeric, it has a strong odor as a result of pungent ketones, including ginger extract, which is mainly used in research studies, the consumed part of the ginger plant is the rhizome or "ginger root" although it is not actually a root (**Brett White, 2007**)

As for its uses, it has been classified by the US food and drug Administration (**FDA**) as a food additive but has been studied primarily as a treatment for nausea, but it is also used as an anti-inflammatory and pain reliever, as the ancient Chinese used it as an aid to digestion, nausea and treatment of rheumatism (**Kathi J Kemper, 1999**), the effectiveness of ginger root has been widely documented for preventing nausea, dizziness

9-1-3-Lavender

Lavender or as it is called the mother of oils due to its chemical composition and unique smell (**Becky Upham, 2020**), the genus lavender (lavandula) is native to the lands around the Mediterranean as well as Southern Europe, North Africa, the Middle East, as far as South-Eastern India and Southeast Asia (**Peir Hossein Koulivand *et al*., 2013**)

Lavender oil consists of linalyl acetate in large proportion, linalool, camphor, terpinen-**4**-ol, **1¸8**-cineole and beta-ocimene, lavender oil also shows anti-bacterial and anti-fungal properties (**Svetlana Perovic *et al*., 2019**)

Lavender essential oil is considered a complementary medicine and is used as an additive to many complementary medicines, and cosmetics such as perfumes and also used in cleaning materials, anti-inflammatory and soothing (**Heather MA Cavanagh et Jenny M Wilkinson, 2005**)

II- Anxiety

A person often faces problems and risks that affect his normal life, as he has a natural reaction known as anxiety, but if this feeling is not related to any clear raison, then this is a disease called anxiety syndrome **(Klein & Pine, 2001).**

So what is this disease, what are its most important symptoms, causes and ways to treat it, and what is the role of aromatherapy in this?

1-Definition of Anxiety

Anxiety is a state of internal disturbance that is embodied in psychological phenomena such as tension, fear, and physical phenomena such as trembling and high blood pressure due to a group of cognitive and behavioral elements that make a person feel psychological discomfort and fear for a specific reason or even without a reason. Anxiety may be severe or mild **(Hoehn-Saric R McLeod DR, 1985).**

There are many types of anxiety, including Generalized Anxiety Disorder (GAD), Obsessive-Compulsive Disorder (OCD), Post-Traumatic Stress Disorder (PTSD), Social Anxiety Disorder(SAD) .....**(Crino RD et Andrews G, 1996)**

2- Symptoms of Anxiety

Anxiety Symptoms vary from person to person, but the way in which the body reacts with this matter be specific through the psychological and physical changes that can observe the sick person, so these are the most prominent symptoms that most of those suffering from anxiety diseases share:**(Rynn MA, Brawman-Mintzer, 2004)**

- Breathing disorder **(Diana Wells,2020)**
- Inability to concentrate **(Testa .A *et al.*, 2013)**
- Sweating and Trembling **(Folk J, Folk M,2009)**
- Experiencing gastrointestinal (GI) problems **(De Heer. EW *et al.*, 2014)**
- Having an increased heart rate **(Testa .A *et al.*, 2013)**
- Panic, fear, and uneasiness **(De Heer. EW *et al.*, 2014)**
- Headache, dizziness, depression **(Popa SL, Dumitrascu DL, 2015)**
- Weak immune system **(Barker P,2003)**
- Body muscle tension. **(Popa SL, Dumitrascu DL, 2015)**
- Having trouble **(Folk J, Folk M,2009)**
- Dry mouth **(Folk J, Folk M,2009)**

3-Causes of Anxiety

Although most of the studies conducted by scientists to determine the apparent cause of anxiety disease did not give specific results, there are several factors that can be a direct cause of the disease, including psychological and other biological causes, and these are the most prominent reasons that were suspected to be related to cases of anxiety diseases:**(Tillfors, 2004).**

- Psychological stress and pressure that lasts for a long time **(Tillfors, 2004).**
- Going through difficult events, especially during childhood (**Erwin *et al.*, 2006).**
- Overthinking about family and work problems **(Grant et al., 2005).**
- Imbalances in brain chemistry without a clear reason, especially neurotransmitters, which are often caused by genetics **(Stein *et al.*, 1998).**

- Side effects of some medications, such as epilepsy drugs **(Tillfors, 2004).**
- Thyroid problems **(Grant *et al*., 2005).**
- Some rare brain tumors that damage areas of the brain **(Stein *et al*., 1998).**
- A family history of this disease may cause anxiety (**Erwin *et al*., 2006)**
- Excessive consumption of alcohol and caffeine and then stop suddenly **(Tillfors, 2004).**

4- Diagnostic of Anxiety

The diagnosis of anxiety at the request of the doctor when the patient shows some symptoms that were previously mentioned and described, where the patient is asked several questions to make sure that these symptoms are related to anxiety no other diseases, where the doctor asks about the drugs that are taken or the consumption of alcohol, coffee or Smoking **(Phillips KA*et al.*,2010)**, then a physical examination and a set of self-tests are performed to see the patient's reaction to a specific situation, and through which he can determine that he suffers from anxiety**(Vollebergh WA *et al.*,2001).**

If the doctor suspects that the patient is showing signs of this disease, he requests some clinical tests, such as urine and blood tests and x-rays to confirm whether there is a biological cause for this disease **(Testa A *et al.*,2013)**, the latter performs a comprehensive psychological questionnaire about the patient's emotions, concerns, and problems, and since when he suffers from these symptoms and the time when they increase in severity, and therefore it is confirmed that there is a psychological cause for this disease or no (**World Health Organization,2009).**

5- The effect of Anxiety disease on the brain

When suffering from anxiety, the first organ in the body is exposed to negative influences is the brain due to the presence of glands, hormones and neurotransmitters inside it, causing a series of changes that reduce the efficiency of the role it plays **(Drevets WC, 2001).**

Several important parts of the brain are involved in responding to feelings of anxiety, the most important of which are the amygdala which is located deep in the brain and is a communication center that processes incoming sensory signals**(University of Idaho College of Science, 2004)**, it consists of a bundle of neurons, and the hippocampus, which is a region from the brain responsible for memories and emotions.**(Drevets WC, 2001).**

When anxious, the hypothalamus activates the sympathetic nervous system and the adrenal cortex, which combine to produce a rapid response that increases glucose levels and stop certain systems that are not essential for the brain's overall focus. (**Susanne Fischer, 2021).**

Whether the feeling of anxiety is due to an obvious reason or not, the brain releases a wave of chemicals such as noradrenaline and cortisol **(Olpin M, 2020)** that make the heart pump faster for more blood and oxygen to flow. These chemicals also affect rational thinking, as the electroencephalograms showed large amounts of high brain waves in the right lobe **(Olpin M, 2020).**

Anxiety damages the connections between the amygdala and the prefrontal cortex. In the normal case, the amygdala stimulates the brain, which in turn stimulates the frontal lobe responsible for logical thinking **(Drevets WC, 2001),** giving a rational response but with the increase in chemicals caused by anxiety, the link between the amygdala and the frontal lobe weakens, and thus the rational part of the brain is not stimulated, which leads to irrational thoughts and incorrect behavior **(Bishop SJ *et al.*, 2004).**

Anxiety also causes a contraction of the hippocampus responsible for memories **(Linda Mah *et al.*,2016),** which makes it difficult for him to retain memories store only bad memories associated with the occurrence of the disease, such as failure, sadness, and abandonment of everything related to happiness **(Bystritsky A,2018).**

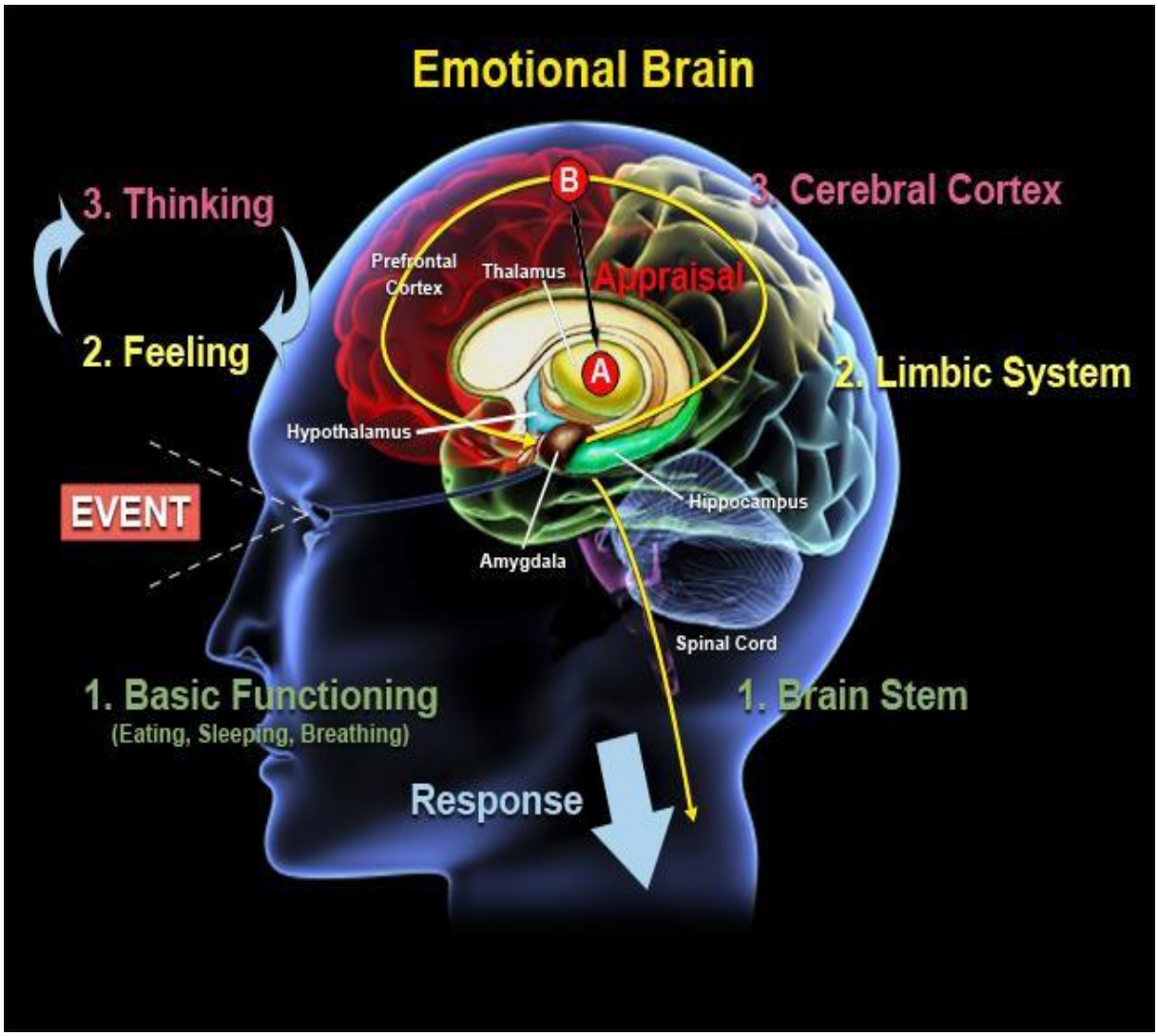

Figure 26: The most important areas affected by anxiety in the brain (**karengosling website)**

6- Treatments and prevention of anxiety

The treatment of anxiety is related to the diagnosis carried out by the specialist doctor, as there are two main types of treatment methods, either pharmacological treatment through drugs, essential oils of plants, or psychotherapy **(Foa, E. B *et al.*, 2011).**

a-drug treatment for anxiety

There are several medications used to treat anxiety and relieve its symptoms, including sedatives and antidepressants**(Stein MB et Sareen J, 2015)** that work to restore the balance of chemical elements inside the brain, such as benzodiazepines or fluoxetine, which balances the action of neurotransmitters**(Stein MB et Sareen J, 2015)**.

These medications are prescribed in specific doses based on the doctor's assessment of the symptoms that appear on the patient **(Barlow, D. H, 2002).**

b-Psychotherapy for anxiety

- Anxiety is treated psychologically through psychologists who conduct special sessions to reduce the symptoms of the disease, such as the cognitive behavioral therapy (CBT) approach, which is used to identify the causes of the disease and try to alleviate them through activities such as practicing relaxation sports **(Deacon, Abramowitz, J. S, 2004).**

- A healthy lifestyle is the most important way to prevent this disease, such as good sleep, maintaining daily activity by walking, exercising regularly, and avoiding smoking and alcohol **(Moreno-Peral P *et al.*, 2017).**

7-Role of phytotherapy against anxiety

- Alkaloids are one of the most important anxiety-reducing plant components **(Perviz *et al.*, 2016)**, as they reduce the elevated anxiety-induced acetylcholine in the hippocampus and prefrontal cortex, which contributes to mood improvement **(Minor *et al.*, 2016).**
- Diterpene alkaloids improve the activity of the neurotransmitter serotonin, and Punaravin E alkaloid inhibits Monoamine oxidase in the brain and lowers the level ofcorticosterone in the plasma to reducing anxiety **(Dhingra and Valecha, 2014).**
- Phenols activate GABA receptors, which work to relax and reduce symptoms of anxiety **(Bouayed J, *et al.*, 2007).**
- The effect of phenols is similar to that of antidepressants, as they are antioxidants that block the absorption of neurotransmitters inside the brain, and it is the best way to prevent anxiety **(Pan Xu *et al.*, 2016).**
- Flavonoids work to remove the effects of heavy metals that can cause diseases such as anxiety, as compounds derived from flavonoids such as luteolin; baicalin and hesperidin contribute to protecting the mitochondrial wall, modulating the activity of the enzyme acetyl cholinesterase and regulating the work of calcium and potassium channels, which helps restore a stable system nervous (**Singh B *et al.*, 2012).**
- Flavonoids inhibit monoamine oxidase enzymes, which work to uptake serotonin into the nervous system, which leads to reducing the effects of anxiety **(Farida Larit *et al.*, 2018).**

7-1 The role of aromatherapy against Anxiety

Aromatherapy through essential oils is considered the best alternative method for drug treatment that is described by nutrition experts and specialists in alternative medicine, as many anxiety patients resort to it, especially those who are afraid of the side effects of drugs and psychological treatments because herbs are safer **(Bharkatiya M *et al.*, 2008),**

So how effective can this treatment be, and how can essential oils reduce the effects of anxiety?

7-2 The effect of essential oils on relieving anxiety

Essential oils are one of the most effective treatment methods that have proven to be very effective in relieving anxiety, as a study conducted by aromatherapy specialists showed that the effect of essential oils, whether through inhalation or application on the skin, was more effective than other treatment methods, medication or psychotherapy **(Kanany.M *et al.*,2011).**

According to a study conducted by alternative medicine specialists, when the patient inhales essential oils, part of them travels through the lungs and passes through oxygen and blood to the rest of the other organs **(Babashahi M *et al.*, 2010),** while the large part of it passes through the nose and activates the nerve endings in it, so the latter sends a message to the olfactory nerve inside the brain, which is connected to the temporal lobe, where the amygdala and the hippocampus are located. Both are activated, and then the pituitary gland is activated, which secretes hormones that affect the patient's condition **(Herz RS, 2009).**

When massaged, these oils are absorbed and transmitted through the blood to all organs of the body **(Herz RS, 2009).**

7-2-1 Jasmine (*jasminum officinale*)

The jasmine tree is a beautiful type of flowering tree characterized by a yellow and red color, its length ranges between 3 and 4 meters, and it has a strong aroma consisting of climbing branches and falling green leaves **(A.K. Singh, 2006).**

Jasmine has been used since ancient times in many fields, especially the manufacture of sedative medicines, the manufacture of food products and the perfume industry **(Bedi, B. M,1971).**

Jasmine essential oil is extracted using two methods:

a-Extraction by enfleurage **(Fakhry, H. A., 2014).**

b-Solvent extraction **(Fakhry, H. A., 2014).**

c-Distillation methods **(Fakhry, H. A., 2014).**

- The essential oil of jasmine consists mainly of diterpene alcohols, benzyl acetate, benzyl benzoate, eugenol, geraniol, and linaloite and methyl jasmonate **(Blanch *et al.*, 2009).**
- A study conducted in 2013 showed that jasmine oil reduces anxiety without the appearance of signs of drowsiness on patients. In 2017, a positive effect of jasmine oil was discovered on a group of mice, which were noted to have become calm in the corner of the cage-**(Kuo TC, 2017).**
- When jasmine oil is inhaled, it passes directly from the nose to the brain and affects a chemical called GABA by enhancing its presence in the brain secretions, which leads to a feeling of calm, calms anxiety and relaxes muscles **(Semyanov A *et al.*, 2004).**
- Also, many researches showed that jasmine oil helped calm a group of people and showed a better effect than antidepressants in treating negative symptoms of anxiety such as cramping and high blood pressure **(Lis-Balchin *et al.*, 2002).**

7-2-2 Chamomile (*matricaria chamomilla*)

- Chamomile is an annual tree that has been known since antiquity and grows abundantly in Southern Europe. Its leaves are long and its stems are branched, up to 60 cm high **(Singh *et al.*, 2011).**
- There are two types, German and Roman. They are used in many fields, such as medicine, perfumery and cooking **(Singh *et al.*, 2011).**
- Chamomile oil is extracted by distillation or solvent extraction **(Mwaniki, J. M. et Mbugua, S. N, 2007).**
- Chamomile oil contains Chamazulene, alpha-Bisabolol oxide A, N-in-dicycloether, Bisabolone oxide A, Germacrene Octanal D and 24 other ingredients **(Bakkali, F *et al.*, 2008).**
- In a 2016 study by Phytomedicine, chamomile was shown to reduce the effects of anxiety in the medium term **(John R *et al.*, 2016).**

- The American Research Center also confirmed that when consuming chamomile, whether through drinking or inhaling, the flavonoid element found in chamomile called Apigenin has an effect on brain receptors like the effect of Valium, and it helps calm patients without any side effects **(Awad R *et al.*, 2007).**
- Chamomile after inhalation also contributes to increasing the synthesis of the amino acid glycine, which helps calm and relax muscles, in addition to containing antioxidants that promote the stability of nerve cells and help the brain to perform its roles effectively **(American Chemical Society, 2005).**

7-2-3 Lemon balm (*Melissa officinalis*)

- Lemon balm or Melissa officinalis is a plant of the mint family that was widely used in the Middle Ages. It is found in Europe up to a meter in length. Its leaves are toothed and wrinkled, light green in color (**Abuhamdah *et al.*, 2008).**
- Melissa is used in the fields of nutrition, pharmaceutical and cosmetic industries **(Tsoukalas *et al.*, 2019).**
- Lemon balm oil is extracted by steam distillation **(National Association for Holistic Aromatherapy).**
- Lemon balm oil consists of terpenes, tannins, eugenol, citral, citronellal, and geraniol **(Ehrlich, Steven D, 2017).**
- A study in an Australian journal revealed that lemon balm oil has an effective role in reducing anxiety and its symptoms and improving mood, as the components of lemon balm oil were placed in the patients' drink, which led to the disappearance of symptoms such as the digestive problems **(Kennedy D.O *et al*., 2004).**
- Research and analyzes have revealed that rosmarinic acid, which is a component of lemon balm oil, maintains the presence of GABA in the brain, reducing neuronal activity, which leads to relaxation **(Dae Young Yoo *et al*.,2011).**
- After inhaling or drinking lemon balm oil, it goes directly to the brain and inhibits the action of the GABA-T enzyme that destroys GABA, so this is the reason for maintaining the proportion of this neurotransmitter, which affects the patient's mood effectively **(Kennedy, D.O.*et al*., 2004).**

WORK SUMMARY

Chapter 01

1-Phytotherapy

The science that studies the treatment or prevention of diseases by using medicinal plants or their extracts by exploiting the biological effect of the active components of these plants.

2- Types of phytotherapy

There are several types of phytotherapy that differ according to the type of medicinal plants, the method of extracting medicinal components, or the purpose of their use, which is:

- Aromatherapy
- Gemotherapy
- Herbalism
- Chinese Phytotherapy
- Pharmaceutical phytotherapy
- Homeopathy

3-Indications for phytotherapy

Phytotherapy is used to solve many health problems that affect humans, whether mental or organic diseases including them:

- Joint pain
- Depression and mood disorders
- Blood circulation disorders
- memory problems
- Anemia
- Gastrointestinal diseases

II-Medicinal plants

Any plant that has been shown to contain a number of active substances that have a therapeutic and medical impact on a particular type of disease.

3-The active substance of medicinal plants

3-1-Alkaloids:

Alkaloids are chemical compounds of natural origin mostly of vegetable origin, but there are also some animals and bacteria that produce alkaloids.

3-2-Flavonoids:

Flavonoids are hydroxyl compounds of natural origin in plants.

3-3-Phenols (component of medicinal plants)

Phenols are natural compounds in plants, produced by secondary metabolism

2- Use of medicinal plants

Generally, the use of medicinal plants is in two forms:

- Raw Form: Such as vegetable oils, herbal extract, soaked.
- Pure shape: through the active substance of the plant.
- use in cooking
- Used as an ointment against inflammation and skin diseases.
- Manufacture of clothing.
- Use medically in the preparation of surgical dressings.

4-Action of medicinal plants

Alkaloids, terpenoids and secondary metabolites (SM), they modify and affect an identical molecular target in animals or humans, where these targets are often enzymes or neurotransmitters.

secondary metabolites may they have pharmacologically active properties, including antibiotics and antivirals, metabolites can interfere with biological activities because they have more than one active functional group such as epoxides, sh-groups, aldehydes.

Proteins are the molecules most targeted by secondary metabolites; secondary metabolites have a reactive group,

III-Aromatherapy

Aromatherapy is the alternative medicine that relies mainly on the essential oils of plants through various methods of application, which gives a positive effect on several diseases.

1-Indications and uses of aromatherapy:

1. Treating anxiety, depression and stress:
2. Headache and migraine treatment:
3. Improving immunity and treating infections:
4. Rebalancing the hormones:
5. Promote healthy hair and skin

2-Types of aromatherapy:

1. Massage aromatherapy:
2. Cosmetic aromatherapy:
3. Medical aromatherapy:

3-Essential oils:

Essential oils are oily extracts extracted from plants or some of their parts (leaves, roots, bark...).

4-Compositions of essential oils:

- **Aldehydes:**
- **Alcohol:**
- **Esters:**

5-Production and extraction of essential oils •

1. **Hydro distillation**
2. **Steam Distillation**
3. **Solvent Extraction**
4. **Cold Pressing**

5-The role of essential oils against neurological diseases

- Biochemical activity: the biochemical receptors of our body capture the molecules of essential oils, which leads to a therapeutic action
- Energy activity: essential oils exchange electrons with the environment in which they are found, which modifies energy flows.
- Informational activity: the scent of essential oils acts on the brain by triggering psychological and physiological reactions.

The essential oils that contain 1, 8-Cineole which is considered as antinociceptive, smooth muscle relaxant and neuronal excitant by reducing the excitability of peripheral neurons by blocking the voltage-dependent current Na + and inhibiting potassium channels.

The essential oils that contain Menthol, which have anticonvulsant, antinociceptive and anesthetic activities by the agonist of GABAA receptors hippocampal neurons. The protective effect of lavender oil against cerebral ischemia as linalool inhibits the release of acetylcholine and alters the function of the channel at the neuromuscular. junction.

Chapter 02

Nervous system: A group of tissues and nervous organs that form a network that controls the biological processes carried out by the body.

The Central Nervous System

Brain: A basic device that ensures the regulation of all vital functions. It receives nerve signals, analyzes them and re-sends other signals to the outgoing nerves.

Cerebrum: The largest part of the brain is responsible for voluntary and involuntary actions, such as speech and thinking. It also regulates the work of the senses.

Spinal Cord: A bundle of closed spinal nerves connected to the brain to transmit a group of neural messages that help to feel sensations and move the body.

Cervical spine

Lumbar spine

Temporal lobe

Frontal lobe

Parietal lobe

Occipital lobe

Brainstem: An area at the base of the brain located between the deep structures of the cerebral hemispheres and the cervical spinal cord that regulates heartbeat and breathing

Midbrain

The Pons

Pituitary gland: a major organ of the neuroendocrine glands and it is small gland located inside a bony structure called (sella Turcica).

Thalamus the thalamus is a structure located centrally in the brain, which is a double structure or is a gray matter structure located above the midbrain.

The Limbic system:

A group of subcortical structures that are particularly concerned with emotion and motivation.

Diencephalon: It is located in the depth of the brain and regulates the relationship between the glandular system and the nervous system.

Medulla oblongata

Pineal gland: tiny organ in the cerebrum that produces melatonin. Also called pineal body and pineal organ.

Posterior fossa: basal side of the skull and houses both the brainstem and the cerebellum, it is the deepest fossil among the other fossils found in the cranial cavity.

Oxidative stress

is a result of the body's inability to get rid of reactive oxygen species due to an imbalance between the production of reactive substances and antioxidants.

The Antioxidant System:

1. **Superoxide Dismutase**
2. **Glutathione peroxidase**
3. **Catalase**
4. **Vitamin E**

Evidence of oxidative stress in neurodegenerative diseases

Oxidative stress enhances the risk of Alzheimer's disease as it has been found that oxidative effects within brain tissues such as oxidized proteins, impaired proteasome activity, increased DNA oxidation in mitochondria and nuclei **(**as well as iron oxidation and aging plaques rich in Aβ protein, increase the ability of Aβ protein to bind to selective metals such as Zinc and iron, which are oxidized through metal ions.

1-Nervous Breakdown

State of distress, mental disorder, or illness that occurs to a person suddenly as a result of accumulation of stress.

Causes of nervous breakdown

1. Problems or pressures at work, family..
2. Financial problems such as losing a job or not paying a loan
3. Change in emotional relationships
4. A big and shocking event like the death of a close person

Antidepressants drugs

Drugs that help relieve symptoms of depression and improve the patient's mood by adjusting the proportion of chemicals in the brain.

Types:

Tricyclic antidepressants (TCAs)

Monoamine Oxidase Inhibitors

Specific Serotonin Reuptake Inhibitors

Mechanisms of action of antidepressant drugs

1. Antidepressants modify the chemical imbalances of neurotransmitters that are located in the vesicles of nerve cells in the brain.
2. The outer end of a nerve releases neurotransmitters such as dopamine, norepinephrine, or serotonin.
3. Monoamine oxidase inhibitors block the absorption of one of these neurotransmitters, serotonin, through special selective receptors that inhibit the work of the enzymes responsible for its degradation.
4. Tricyclic antidepressants boost neurotransmitters called norepinephrine.

Adverse effects with antidepressants

1. Severe Nausea and Diarrhea
2. Headache, Dizziness and Insomnia
3. Serotonin syndrome:

Chapter 3

I . Alzheimer

Definition

-A neurodegenerative disorder that spreads gradually and causes death

-It begins with an initial impairment of memory, and progresses to a total loss of thinking, cognition and memory. It leads to the accumulation of Beta-amyloid plaques and tau in the brain and the formation of neurofibrillary tangles

Symptoms

1. a gradual loss of memory
2. Symptoms of recognition problems
3. Difficulty walking and stumbling

causes

-The first and main reason is still unknown

The role of phytotherapy against Alzheimer's

-Plants that contain antioxidants such as flavonoids and vitamin E and C reduces oxidative stress

-Some plants such as ginseng and ginkgo biloba have positive therapeutic effects against some symptoms of Alzheimer's

The effect of active substances

1-Alkaloids: it is an important source for the treatment of various brain disorders

Approved cholinesterase inhibitors by the FDA are from Alkaloids

2-Flvonoids: acts as an acetylcholinesterase (AchE) inhibitor and improves cognition

3-Phenolic compounds: it has effects on the pathways of accumulation of beta plaques in the brain

1. The essential oils of lemon balm and lavender have positive effects on cognition
2. Some essential oils help improve some symptoms such as insomnia
3. Side effects of essential oils are almost non-existent

4. The essential oils of lemon balm and lavender have positive effects on cognition
5. Some essential oils help improve some symptoms such as insomnia
6. Side effects of essential oils are almost non-existent

II-Anxiety

A state of internal disorder, manifested in psychological phenomena such as fear and physical phenomena such as tremor and high blood pressure

A state of internal disorder, manifested in psychological phenomena such as fear and physical phenomena such as tremor and high blood pressure

Symptoms

1. Shortness and rapid breathing
2. Trembling
3. Increase in heart rate
4. Headache and dizziness

Causes

1. Psychological stress that lasts for a long period because of going through difficult events
2. Over thinking about work and family problems
3. Imbalances in brain chemistry special neurotransmitters, where these imbalances often occur due to genetics
4. Side effects of some medications, such as headache medications
5. Family history of this disease

The role of phytotherapy against Anxiety

-**Alkaloids**: Reduce the high anxiety caused by acetylcholine in the hippocampus and prefrontal cortex which improves mood

-**Diterpene Alkaloids**: Improved activity of the neurotransmitter serotonin

-**Punaravin E alkaloid**: It inhibits monoamine oxidase in the brain and lowers the level of corticosterone in the plasma to reduce anxiety

-**Phenols**: GABA receptor activation, phenols are similar to antidepressants as it is an antioxidant that prevents the absorption of neurotransmitters inside the brain

-**Flavonoids**: works to remove traces of heavy metals that may cause anxiety such as Luteolin, and flavonoids inhibits the monoamine oxidase enzymes that act to reuptake serotonin, thus reducing the effects of anxiety.

The effect of essential oils

-Especially by inhalation where the odor molecule passes through the nose and activates the nerve endings, and leads to sending a message to the olfactory nerve inside the brain, where the amygdala and the hippocampus are activated, and finally the activates of the pituitary gland,

Scientific article:

Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-161088
IOS Press

Review

Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease

Eric Tönnies[a] and Eugenia Trushina[a,b,*]
[a]*Department of Neurology, Mayo Clinic Rochester, MN, USA*
[b]*Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, MN, USA*

Accepted 22 November 2016

Abstract. Alzheimer's disease (AD) is a devastating neurodegenerative disorder without a cure. Most AD cases are sporadic where age represents the greatest risk factor. Lack of understanding of the disease mechanism hinders the development of efficacious therapeutic approaches. The loss of synapses in the affected brain regions correlates best with cognitive impairment in AD patients and has been considered as the early mechanism that precedes neuronal loss. Oxidative stress has been recognized as a contributing factor in aging and in the progression of multiple neurodegenerative diseases including AD. Increased production of reactive oxygen species (ROS) associated with age- and disease-dependent loss of mitochondrial function, altered metal homeostasis, and reduced antioxidant defense directly affect synaptic activity and neurotransmission in neurons leading to cognitive dysfunction. In addition, molecular targets affected by ROS include nuclear and mitochondrial DNA, lipids, proteins, calcium homeostasis, mitochondrial dynamics and function, cellular architecture, receptor trafficking and endocytosis, and energy homeostasis. Abnormal cellular metabolism in turn could affect the production and accumulation of amyloid-f3 (Af3) and hyperphosphorylated Tau protein, which independently could exacerbate mitochondrial dysfunction and ROS production, thereby contributing to a vicious cycle. While mounting evidence implicates ROS in the AD etiology, clinical trials with antioxidant therapies have not produced consistent results. In this review, we will discuss the role of oxidative stress in synaptic dysfunction in AD, innovative therapeutic strategies evolved based on a better understanding of the complexity of molecular mechanisms of AD, and the dual role ROS play in health and disease.

Keywords: Alzheimer's disease, amyloid-f3, antioxidants, caloric restriction, exercise, mitochondria, mitohormesis, neurotransmission, oxidative stress, synaptic function, tau protein

MOLECULAR HALLMARKS OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) affects more than 5 million Americans, with numbers expected to grow as the population ages [1, 2]. Most AD cases are sporadic where the origin of the disease is not known but might be influenced by multiple factors including environmental exposure, genetic risk factors, mitochondrial haplotypes, age, and sex [2–4]. About 1% of cases are associated with familial mutations in the genes that encode either a transmembrane amyloid-f3 protein precursor (Af3PP), or proteins presenilin 1 (PS1) and presenilin 2 (PS2), which are directly involved in the Af3PP processing. While cleavage of Af3PP at the plasma membrane by the α-secretase occurs without formation of pathologic amyloid-β (Af3) peptides, cleavage with f3- and)'-secretases leads to the release in the extracellular space of Af3 peptides with 40 or 42 residues where $Af3_{42}$ is more prone to aggregation and is the major component of extracellular amyloid plaques [5, 6]. Along with

*Correspondence to: Eugenia Trushina, PhD, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA. Tel.: +1 507 284 8197; Fax: +1 507 284 3383; E-mail: Trushina.Eugenia@mayo.edu.

the formation of extracellular aggregates, Af3 peptides are present in neurons [5, 7]. Multiple studies conducted *in vitro* and *in vivo* using human tissue and transgenic mice demonstrated that intracellular Af3 accumulates prior to the development of extracellular plaques where it specifically affects synaptic function leading to a profound memory deficit [8–10]. The existence of intraneuronal Af3 could be explained by multiple mechanisms. Besides the plasma membrane, Af3PP is present at several intracellular sites including the trans-Golgi network [11], endoplasmic reticulum (ER), and endosomal, lysosomal [12], and mitochondrial membranes [13] where Af3 could be generated via f3- and γ-secretase cleavage. In addition, secreted Af3 peptides could be internalized via receptor-mediated or/and receptor-independent endocytosis [14–16]. Extensive studies also support the notion that soluble Af3 oligomers represent the most toxic species that affect multiple early molecular mechanisms leading to synaptic dysfunction in AD [15].

Intracellular neurofibrillary tangles (NFT) represent another hallmark of AD. Tau is a microtubule stabilizing protein. When it becomes hyperphosphorylated, it dislocates from the microtubules leading to their destabilization and a disruption of neuronal trafficking machinery [17]. Af3-induced translocation of Tau to neuronal spines is associated with synaptic dysfunction early in AD pathogenesis [18]. The definitive diagnosis of AD can only be done by examining the postmortem brain tissue based on the presence of extracellular plaques formed by Af3 peptides, intracellular NFTs comprised of hyperphosphorylated Tau protein (pTau), Af3 deposits in blood vessels, neuronal and synaptic loss, and significant atrophy in selective brain regions involved in cognitive function (hippocampus, entorhinal, and frontal cortices) [19]. The identification of familial AD mutations in *APP*, *PS1*, and *PS2* genes gave rise to the amyloid cascade hypothesis that considered the formation of Af3 a culprit of the disease. While excessive production of Af3 peptides is observed early in patients that develop AD and is essential for AD pathology [20], it is not sufficient. Some aged individuals have significant Af3 load, but do not develop cognitive impairment [21, 22]. Recent studies conducted using positron-emission tomography (PET) and novel tracers that allow imaging of both amyloid and Tau distribution in the brain of living individuals suggest that there is a relationship between Tau protein deposition, Af3 plaques, and neurodegeneration [23]. Based on the pattern distribution and the manifestation of cognitive symptoms, it appears that the widespread presence of Af3 in the brain does not lead to the development of AD without Tau being present in the affected areas. These observations support the idea that the synergistic interaction between Af3 and Tau is essential to trigger neurodegeneration in AD [24, 25]. While this provides important insights into AD patient's diagnostic and prognostic criteria, early molecular mechanisms leading to the accumulation of Af3 and pTau or driving factors that promote their spreading in the brain remain poorly understood hindering the development of efficacious therapeutic interventions [26–29].

THE ROLE OF OXIDATIVE STRESS IN ALZHEIMER'S DISEASE

In search for the underlying mechanisms of AD, the amyloid cascade hypothesis that dominated the field of AD research for the past decades has been challenged [30–32]. An alternative explanation of the disease mechanism has emerged from the observations linking mitochondrial dysfunction and increased production of reactive oxygen species (ROS) to the development of AD. The mitochondrial cascade hypothesis states that in sporadic, late-onset AD, loss of mitochondrial function associated with age affects the expression and processing of Af3PP initiating Af3 accumulation [33]. Mitochondrial dysfunction has been well documented in AD [34, 35]. Abnormal mitochondrial axonal trafficking is already observed in embryonic neurons from multiple transgenic mouse models of familial AD with additional abnormalities in fission, fusion, and function detected prior to the development of amyloid plaques or memory impairment [36–50]. Brain glucose metabolism measured using fluorodeoxyglucose-positron emission tomography (FDG-PET) is reduced prior to the onset of disease in several groups of at-risk individuals including patients with mild cognitive impairment (MCI), a prodromal stage of AD, and in carriers of the apolipoprotein E epsilon-4 (ApoE4) allele, a strong genetic risk factor for late-onset AD. However, this hypometabolism does not correlate with an increase in brain Af3 deposition [51–53]. Furthermore, disruption in glucose metabolism associated with early mitochondrial dysfunction detected in multiple animal models and AD patients [38, 41, 43, 48, 54–60] may also be a direct determinant of oxidative stress and synaptic dysfunction that contribute to early disease mechanisms before any evidence of Af3 or

Tau pathology [48, 61–63]. In the brain, the free energy necessary to drive most cellular reactions is primarily produced in mitochondria from the oxidation of glucose under aerobic conditions (Fig. 1). Oxidative stress, which is defined as 'an imbalance in pro-oxidants and antioxidants with associated disruption of redox circuitry and macromolecular damage' [64], is associated with increased production of ROS and reactive nitrogen species (RNS) including superoxide radical anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (HO^-), nitric oxide (NO^-), and peroxynitrite ($ONOO^-$). While there are multiple sources of ROS production in the cell including ER, peroxisomes, a family of NADH oxidases, and other enzymes such as monoamine oxidases [65, 66], mitochondria are the largest contributor to ROS production (Fig. 1) [67, 68]. During oxidative phosphorylation, H_2O_2 and O_2^- are produced as byproducts in mitochondria primarily by complexes I and III [69]. Under normal conditions, the antioxidant enzymes acting as free radical scavengers mediate levels of ROS. These include superoxide dismutases (SOD), glutathione peroxidase (GPX), glutaredoxins, thioredoxins, and catalase (Fig. 1). Additional mechanism of protection against oxidative stress involves the activation of nuclear factor erythroid-2-related factor 2 (Nrf2). Nrf2 is a transcription factor negatively regulated by its binding to the cytoplasmic repressor and stress sensor Kelch-like ECH associated protein 1 (KEAP1), which acts as a substrate adaptor to mediate ubiquitination and degradation of Nrf2 by the E3 ubiquitin ligase Cullin-3 [70]. In the presence of electrophiles and oxidants, KEAP1 releases Nrf2 with its subsequent translocation to the nucleus where it activates transcription of cytoprotective genes via promoter sequences containing conserved antioxidant response elements (AREs) [71, 72]. This increases levels of antioxidant enzymes

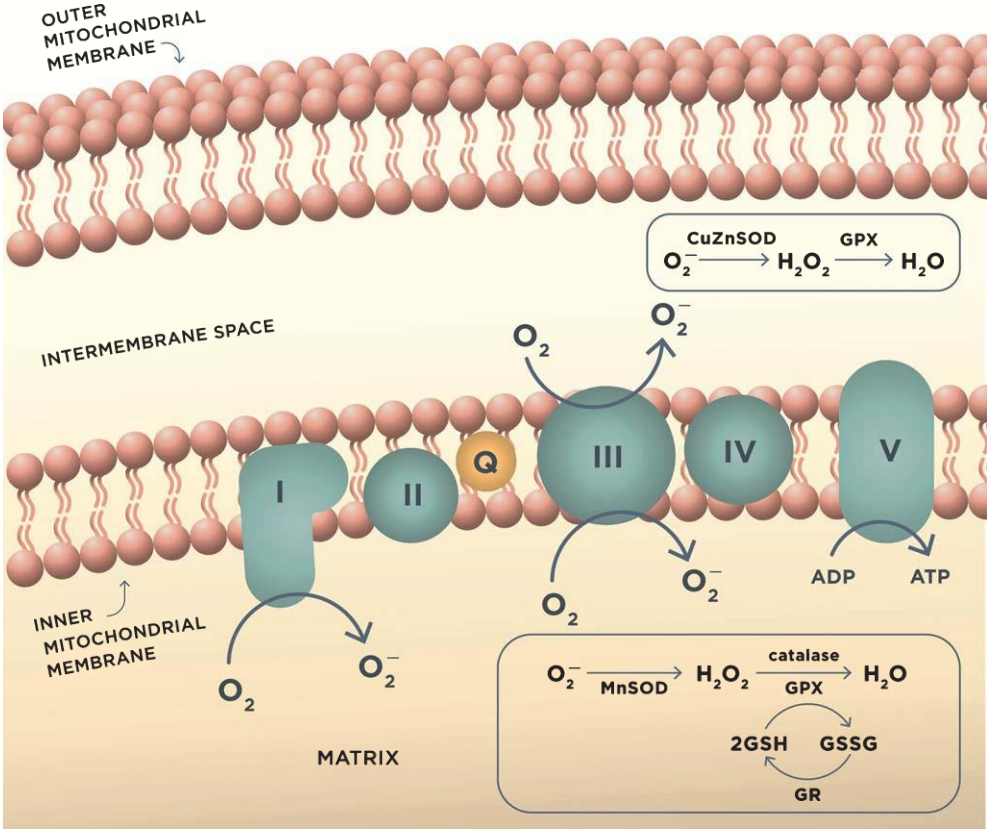

Fig. 1. ROS production in mitochondria during oxidative phosphorylation and antioxidant mechanisms. Complex I and complex III of the mitochondrial electron transport chain are the major sites of superoxide anion (O_2^-) production during aerobic respiration. O_2^- is converted to H_2O_2 by MnSOD or CuZnSOD in the intermembrane mitochondrial space. H_2O_2 is further reduced to water by detoxifying enzymes glutathione peroxidase (GPX) or catalase. GPX uses reduced glutathione (GSH) as the reductant, and the resulting oxidized glutathione reacts with another glutathione molecule to form glutathione disulfide (GSSG), which is restored to GSH by the enzyme glutathione reductase (GR).

These reactions occur in mitochondrial matrix.

and proteins such as glutathione-S-transferase, NAD(P)H: quinone oxidoreductase-1, SOD, GPX, heme oxygenase-1 (HO-1), glutamate cysteine ligase, thioredoxin, and catalase, and also promotes mitochondrial biogenesis ensuring a replacementof damaged organelles [73, 74]. However, there is conflicting evidence on whether Nrf2 is activated in AD. In one study, levels of Nrf2 expression were found to be decreased in AD patients despite the presence of oxidative stress [75]. Other stud-ies reported an increase in the expression of the ARE-related genes in patients with MCI and AD [76, 77]. While the exact mechanism is presently unknown, these discrepancies could be associated with the variations in the levels of Nrf2 expression that could be influenced by aging and the disease mechanisms [78].

The balance between ROS production and the antioxidant defense is essential for normal cellular function. However, in AD, the activity of antioxidant enzymes is altered, thereby contributing to the unconstrained accumulation of oxidative damage [79]. When unbalanced, overproduction of ROS combined with the insufficient antioxidant defense leads to oxidative stress [80]. There is evidence that mitochondrial damage resulting in increased production of ROS contribute to the early stages of AD prior to the onset of clinical symptoms and the appearance of the Af3 pathology [80]. In support, markers of oxidative stress including high levels of oxidized proteins, glycosylated products, extensive lipid peroxidation, formation of alcohols, aldehydes, free carbonyls, ketones, cholestenone, and oxidative modifications in RNA and nuclear and mitochondrial DNA were found in postmortem brain tissue and in peripheral systems including cells and isolated mitochondria from people with preclinical or early stages of AD and ApoE4 carriers (Fig. 2) [58, 81–97]. Mitochondrial ROS could collapse mitochondrial membrane potential accelerating ROS production within the same organelle (Fig. 3). As a result, an increase in ROS production in a small subset of organelles could be sufficient to propagate ROS damage to other mitochondria eventually affecting the whole cell [66].

Compelling data demonstrate that in addition to mitochondrial ROS production, abnormal homeostasis of bioactive metals including iron (Fe), copper (Cu), zinc (Zn), magnesium (Mg), manganese (Mn), and aluminum (Al) could be involved in free radical production and oxidative stress influencing Af3 and Tau aggregation [35, 98–100]. Increased levels of Fe, Cu, and Zn were detected using proton

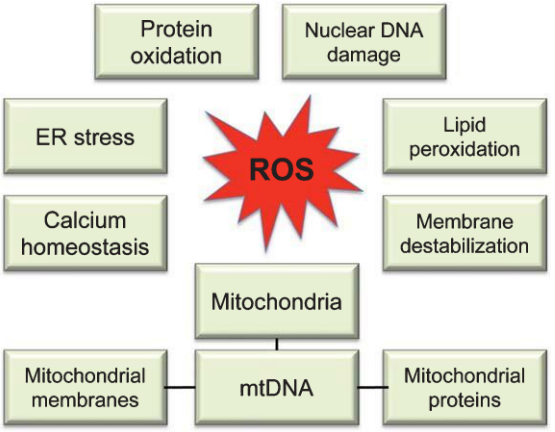

Fig. 2. Molecular targets of ROS. While multiple sites in the cell can contribute to ROS production, uncontrolled ROS generation in mitochondria could impair a major source of energy in the cell resulting in detrimental consequences to the whole cellular environment. Intermediate levels of ROS can gradually affect multiple cellular functions including loss of synaptic activity, while critically damaged mitochondria can trigger a release of cytochrome *c* activating apoptosis.

induced X-ray emission, immunohistochemistry, and synchrotron X-ray fluorescence in close proximity to the amyloid plaques in the brain tissue of AD patients and transgenic mouse models of AD [101–108]. The accumulation of these metals in the first place is thought to originate from the impaired neuronal metal homeostasis affected by aging, and exacerbated by amyloid and Tau pathologies in case of AD [109–111] There is a tight connection between protein misfolding, aggregation, and metal ion homeostasis. In particular, Zn directly affects Af3PP processing by binding to the protein [112], and Al, Zn, Fe, and Cu directly bind Af3 promoting its aggregation [113–115]. Similar, the redox metals could promote Tau phosphorylation, its release from the microtubules, and formation of NFTs [116, 117]. ROS production is facilitated by the redox-active metals including Cu, Fe, and Mn using catalytic reactions similar to the Fenton reaction where metals convert O_2^- and H_2O_2 to HO^- species that are involved in lipid peroxidation [118]. Moreover, a direct binding of Af3 peptides to Cu or Fe has been shown to generate H_2O_2 [119]. Thus, the transition metals and Af3 could synergistically contribute to an increase in oxidative stress and extra-mitochondrial production of ROS. In agreement with a role of metal ions in pathology, restoration of metal dyshomeostasis after application of metal helators [120–122] reduced levels of amyloid plaques and Af3 aggregation, and improved

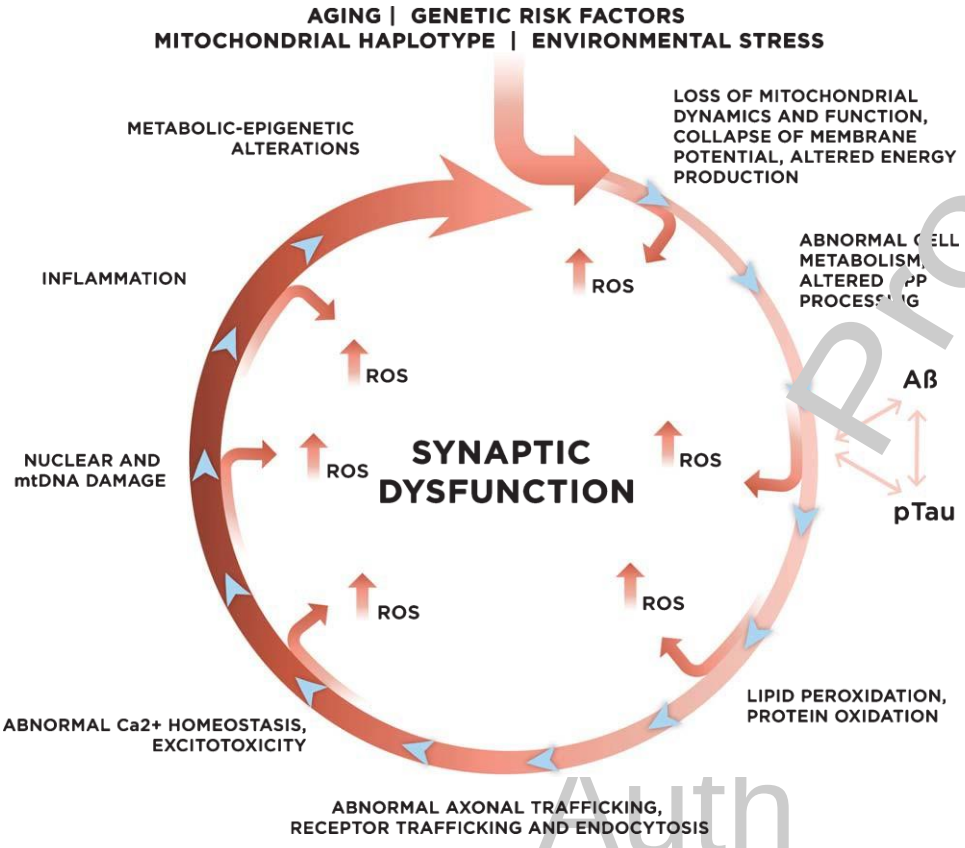

Fig. 3. Genetic and environmental risk factors contribute to the development of late onset sporadic AD. With age, increased mitochondrial dysfunction and ROS production could initiate a vicious cycle where multiple systems and mechanisms affected by ROS exacerbate ROS production, accelerating cellular damage, and leading to synaptic dysfunction.

cognitive performance in humans and mouse models of AD [123].

Another source of non-mitochondrial ROS production directly mediated by Af3 involves microglia activated in the brain during an inflammatory response to the deposition of extracellular amyloid plaques [124]. Further, increased levels of Af3 could accelerate a production of ROS by directly binding to mitochondrial membranes, altering mitochondrial dynamics and function, ultimately leading to the abnormal energy metabolism and the loss of synaptic function [35, 37, 39, 46, 62, 125, 126]. Membrane-associated oxidative stress induced by Af3 peptides perturbs ceramide and cholesterol metabolism that, in turn, triggers a neurodegenerative cascade leading to additional Af3 accumulation, Tau phosphorylation, and clinical disease (Fig. 3) [127–135]. Furthermore, there is a direct link between altered membrane lipids and mitochondrial function, which is detrimental for brain bioenergetics [136, 137]. Strong data generated in animal models and humans suggest an intimate relationship between oxidative stress, Af3 accumulation, and abnormal Tau phosphorylation, where pTau specifically affects the activity of complex I synergistically contributing to the Af3-mediated mitochondrial dysfunction and ROS production [138]. This could explain why accumulation of both Af3 and pTau may be required to initiate neurodegeneration in AD patients [23–25]. Moreover, emerging data suggest that mitochondria-mediated cellular bioenergetics could independently affect Af3PP processing and Af3 production (Fig. 2) [139–145]. However, the details of causal relationship between oxidative stress, mitochondrial dysfunction, and Af3 and pTau accumulation in AD remain to be elucidated. Taken together, these data suggest that altered mitochondrial function, increased oxidative stress, exhausted antioxidant defense, production of Af3 and pTau, which furthermore affects mitochondrial function and ROS production, could represent a "vicious cycle" that with time exacerbates the disease process, eventually leading to neuronal death [47] (Fig. 3).

OXIDATIVE STRESS AND SYNAPTIC DYSFUNCTION IN ALZHEIMER'S DISEASE

Synapses are structurally specialized regions in neurons that propagate an electrical or chemical signal from one cell to another. During neurotransmission, signaling molecules such as glutamate, acetylcholine, dopamine, and others released from the active zones of a presynaptic neuron bind to and activate receptors on a postsynaptic neuron (Fig. 4) [146]. The strength of synaptic transmission depends on changes in neuronal activity where the dynamic nature of synaptic plasticity including long-term potentiation (LTP) and long-term depression (LTD) represents the fundamental mechanism of learning and memory [147, 148]. Neurons have a unique cellular architecture where formation or pruning and maintenance of dendritic spines are essential for neurotransmission and synaptic function (Fig. 4). Synaptic transmission critically relies on the fidelity of multiple cellular mechanisms including biosynthesis of neurotransmitters from amino acids to ensure their availability; the delivery of neurotransmitters to the sites of synapses requiring intact microtubule tracts and vesicle trafficking machinery; formation of synaptic vesicles that encapsulate neurotransmitters preparing for their release via exocytosis; binding of the neurotransmitter to the receptor on the postsynaptic neuron with subsequent activation of cellular response; and the removal of the neurotransmitter from the synaptic cleft after the release (Fig. 4) [149]. In addition, Ca^{2+} plays an essential role in mediating basal synaptic transmission, where an increase of its conductance through voltage gated Ca^{2+}-channels clustered in the presynaptic membrane at the active zone triggers the release of synaptic vesicles [146]. Given the complexity of neurotransmission machinery, factors that affect any step of the process could have a detrimental effect on synaptic

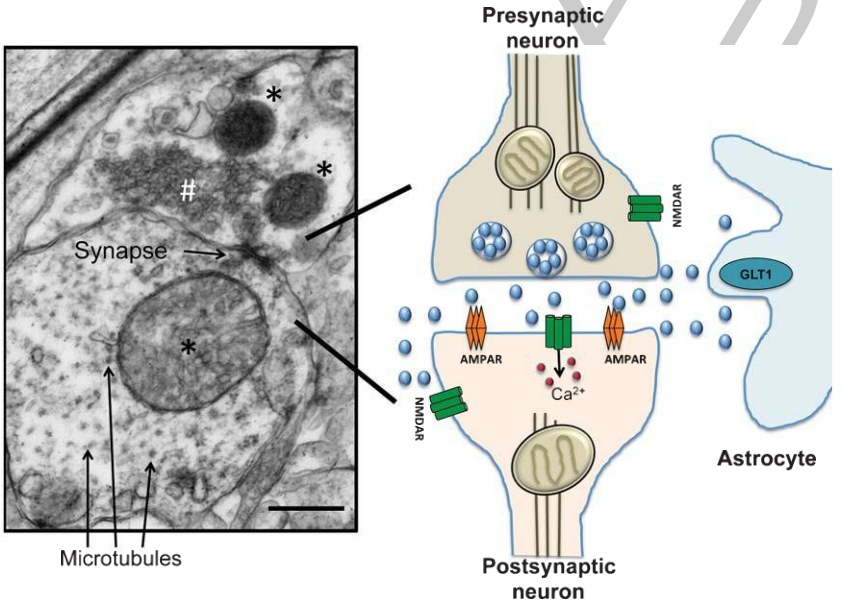

Fig. 4. Structure of a synapse. Left: synapse between two neurons observed in the brain tissue of a wild type C57/Bl6 mouse using transmission electron microscopy (generated in Dr. Trushina laboratory [231]). An arrow indicates electron dense plasma membrane at the synapse. Presynaptic neurons contain a large number of synaptic vesicles (#). Both presynaptic and postsynaptic neurons have mitochondria at the site of synapse (*), which are delivered along the microtubule tracks (indicated with arrows). Scale bar, 0.5 μm. Right: a simplified cartoon of a synapse. Glutamate (blue spheres) released from the presynaptic neuron in a voltage dependent manner, activates the NMDA glutamate receptors present on pre- and postsynaptic neurons. These include AMPA (orange) and NMDA (green) receptors among others. Glutamate is cleared from the synaptic cleft primarily by the glial cells transporters (GLT-1). It is then recycled to neurons, repackaged into synaptic vesicles, and used in another synapse. An inadequate glutamate clearance could lead to the spillover and activation of extrasynaptic NMDA receptors. Memantine is believed to prevent this particular activation. Excessive entry of Ca^{2+} into presynaptic neuron (red spheres) could damage synaptic mitochondria leading to ROS production, altered synaptic transmission and neuronal dysfunction. This phenomenon is called excitotoxicity. Note that mitochondria are delivered to the site of synapse along the Tau-containing microtubule tracks. Destabilization of microtubules could affect mitochondrial localization and energy supply required for proper synaptic function.

function in neurons and, ultimately, on cognitive function.

AD is characterized by progressive memory impairment, which is associated with the inhibition of LTP and enhancement of LTD in the hippocampus [150]. Loss of synapses in the affected brain regions correlates best with cognitive impairment in AD patients and has been considered as the early mechanism that precedes neuronal loss [151–157]. Extensive studies conducted *in vivo* and *in vitro* support a direct relationship between oxidative stress and synaptic dysfunction in AD [39, 126, 158, 159]. In particular, it has been shown that independently and synergistically, ROS, Af3, and pTau affect the activity of *N*-methyl-D-aspartate (NMDA) receptors. The NMDA receptors belong to the ionotropic family of glutamate receptors, which in coordination with α-amino-3-hydroxy-5-methyl-4-isoxa-zolepropionic acid (AMPA) receptors regulate the excitatory synaptic transmission and plasticity in the brain playing an essential role in learning and memory [160, 161]. Activation of NMDA receptors allows Ca^{2+} to enter the postsynaptic cells initiating a cascade of events that is critically involved in establishing LTP. The function of NMDA receptors declines with age, which could explain memory alterations associated with chronological aging. However, in AD, in addition to age-related changes, the expression of neurotoxic Af3 has been shown to reduce the amount of surface NMDA receptors in neurons and in brain tissue of AD mice [162], trigger NMDA-mediated Ca^{2+} influx inducing excitotoxicity and stress-related signaling pathways, exacerbating aging-related increase in oxidative stress, impaired energy metabolism, defective Ca^{2+} homeostasis, and altered regulation of transcription of genes important for neuronal development and plasticity [47, 163]. Memantine, the only FDA-approved drug for AD that is not an acetyl cholinesterase inhibitor, is a noncompetitive, low-affinity antagonist of NMDA receptors. Importantly, memantine has greater affinity to non-synaptic NMDA receptors, which are implicated in excitotoxicity associated with the glutamate spillover and have distinctly different composition of receptor subunits [164, 165]. In addition to the effect on NAMDR, soluble Af3 species have been shown to bind to AMPA receptors promoting their internalization via clathrin-mediated endocytosis after Ca^{2+}-induced activation of calcineurin [166]. Altered internalization of AMPA receptors affects synaptic plasticity inducing synaptic dysfunction and loss of dendritic spines (Fig. 4).

Another type of synapses in the central nervous system utilizes γ-aminobutyric acid (GABA), which is a major neurotransmitter that induces inhibitory effect. In AD, levels of GABA are decreased with disease progression, and reduced levels of expression of GABAergic receptors has also been noted [167]. Degeneration of basal forebrain cholinergic cells that directly project to the cortex and hippocampus is well-documented in AD [168]. The cholinergic system is also implicated in cognitive functioning, especially in attention, memory, and emotion. Extensive data generated in human tissue and multiple animal models of AD demonstrated severe deficit in the activity of multiple acetylcholine synthesizing and degrading enzymes, acetylcholine transporters and receptors involved in synaptic signaling, along with reduction of presynaptic cholinergic markers. These investigations provided compelling evidence for the development of one of the few therapeutic approached currently FDA-approved for AD, cholinesterase inhibitors. This approach allows increasing levels of acetylcholine at synapses by blocking the activity of acetylcholinesterase and butyrylcholinesterase enzymes, which are involved in acetylcholine hydrolysis [169].

Among numerous mechanisms that connect neurotoxic Af3, Tau, oxidative stress, and synaptic dysfunction in AD are excitotoxicity, oxidation of proteins, and lipid peroxidation (Figs. 2, 3). Application of Systems Biology approaches including metabolomics and epigenetics to study early changes associated with AD progression in plasma, CSF, and brain tissue from individuals with different severity of AD and multiple animal models of AD confirmed that major alterations in metabolic networks identified early in disease are directly relevant to changes in neurotransmitter, lipid, and energy metabolism [48, 63, 170, 171]. Af3-induced excitotoxicity associated with an excessive influx of calcium in postsynaptic neurons can lead to a cascade of events that increases ROS production, oxidative stress, Tau phosphorylation, and lipid peroxidation, ultimately leading to synaptic dysfunction (Fig. 3) [172–174]. Alteration of structure and fluidity of plasma membrane associated with lipid peroxidation could affect the organization and function of dendritic spines, signaling pathways, receptor trafficking, and localization [175]. Indeed, alterations in lipid trafficking and metabolism affect membrane fluidity and lipid homeostasis early in ApoE4 carriers [92, 137, 176, 177]. Moreover, lipid peroxidation of mitochondrial membranes could directly affect the dynamic and function

of the organelle leading to reduced energy support at the sites of synapses, which is detrimental for brain bioenergetics [136, 137]. Altered mitochondrial fission, fusion, axonal motility, and function in turn could contribute to ROS production exacerbating synaptic function. As was mentioned earlier, Af3-induced hyperphosphorylation of Tau destabilizes microtubule tracks, which alters axonal trafficking of mitochondria and their synaptic docking, and translocation of Tau to dendritic spines also may have a synergistic effect contributing to NMDA receptor destabilization, excitotoxicity, and increased oxidative stress with detrimental effect on synaptic function (Fig. 3). The role of protein oxidation in the mechanism of AD has been recently reviewed in [4].

THERAPEUTIC STRATEGIES FOR ALZHEIMER'S DISEASE

Currently approved treatments for AD are limited to three cholinesterase inhibitors, donepezil, rivastigmine, and galantamine, and a low affinity NMDA receptor antagonist, memantine. None of these approaches are disease modifying; they do not provide a "cure" but rather symptomatic treatment for some individuals [178]. Moreover, failure of the recent clinical trials focused on production or clearance of Af3 peptides emphasizes the urgency to consider alternative molecular mechanisms in order to design interventions that will delay or alleviate the development of AD [179]. While compelling evidence implicates oxidative stress in the early molecular mechanisms of AD [180], there is no FDA-approved antioxidant therapy for AD. Moreover, while antioxidant experimental therapeutics produced promising results in animal models of AD [181–183], clinical trials either failed or delivered inconclusive results [184]. For example, multiple trials assayed the effect of a strong antioxidant vitamin E (alpha tocopherol) on cognitive function in cognitively normal and generally healthy women 65 years or older [185], in cognitively normal women with preexisting cardiovascular disease or cardiovascular disease risk factors 40 years or older [186], in people with MCI [187], in patients with moderate to severe AD [188], and in individuals with mild to moderate AD [189]. Positive results where statistically significant changes in cognitive performance were achieved after vitamin E administration compared to placebo were found only in people with mild to moderate AD [189]. Importantly, there were no significant differences in the groups receiving memantine alone or memantine plus alpha tocopherol as a combination therapy. Moreover, meta-analysis of 19 randomized trials with vitamin E demonstrated its high toxicity and all-cause mortality at high doses [190]. Inconclusive results were also achieved in an open clinical trial where AD patients stably taking a cholinesterase inhibitor were supplemented with vitamin C and E over 1 year [191]. While oxidation of CSF lipids was significantly reduced after 1 year of the supplementation, the clinical course of AD did not differ between the vitamin-supplemented and the control group. Another failed trial involved the supplementation with vitamin E, C, and α-lipoic acid in patients with mild to moderate AD [192]. Despite a detection of reduced levels of markers of oxidative stress in CSF, a rapid cognitive decline observed in treated group raised significant safety concerns. Similar results were obtained in clinical trials with curcumin, a polyphenolic compound that has been demonstrated to have antioxidant and anti-inflammatory effects in preclinical studies [193]. Comprehensive update on the outcomes of the antioxidant treatments in recent clinical trials was provided in recent reviews [194, 195].

Multiple challenges associated with the design of clinical trials in elderly and the lack of a complete understanding of the molecular mechanism of antioxidant therapy may account for such diverse outcomes. First of all, there is no definitive test to diagnose AD in living individuals. The conclusive diagnosis of AD can only be done after the examination of postmortem brain tissue for the presence of amyloid plaques and NFTs. This introduces some ambiguity in the etiology behind cognitive impairment in the subjects recruited for clinical trials. Next, it is important at what stage of the disease the treatment is administered since some of the interactions may be efficacious only at the early stages. Furthermore, clinical trials in elderly are associated with the relatively small number of participants and short period of treatment, high frequency of death, inconsistent use of medication, and a lack of a follow-up data. However, there are clinical trials in progress that have greater number of participants and extended periods of treatment that may provide better results on the effect of the antioxidant therapy in AD [196, 197]. Along with the trials designed to test efficacy of a single compound found beneficial in preclinical trials, combination therapy for AD may hold a promise [198]. This approach includes treatment with multiple compounds with diverse properties that could improve several mechanisms and functions

altered in AD without adverse side effects. In one of such trials, the administration of a nutraceutical formulation that included folate, alpha-tocopherol, B12, S-adenosyl methioinine, N-acetyl cysteine, and acetyl-L-carnitine to the AD patients over 1 year resulted in stabilization of cognitive function [199]. Similar antioxidant cocktails were shown beneficial in improving memory and cognitive performance in community-dwelling adults without dementia [200, 201].

In recent years, it has become apparent that strategies designed to target total ROS in the organism might not be productive since ROS have dual function. On one hand, increased ROS production contributes to age-related chronic conditions and neurodegeneration [47]. On the other, oxidant species, such as superoxide and hydrogen peroxide, can function as signaling molecules in a broad array of essential redox-dependent signaling pathways that are critical for the organismal survival including epidermal growth factor receptor signaling [202], inactivation of the tumor suppressor PTEN [203], circadian rhythms [204], the inflammatory response [205], and hormetic stress response [206–209]. Redox homeostasis with tight control over levels of ROS production is essential to protect cells from oxidative stress and, at the same time, to ensure presence of the important signaling molecules [210]. Thus, understanding how the dual role of ROS is maintained with age and in the context of different stages of the disease is important for the development of therapeutic approaches that target ROS production and clearance.

Based on the recognized contribution of mitochondria to cellular ROS, the development of novel antioxidants that directly target mitochondria represent a promising approach to mitigate local ROS production compared to the reduction of global levels of ROS. These compounds include coenzyme Q10, idebenone, creatine, MitoQ, MitoVitE, MitoTEMPOL, latrepirdine, methyleneblue, triterpenoids, series of Szeto-Schiller (SS) peptides, curcumin, Ginkgo biloba, and omega-3 polyunsaturated fatty acids. These mitochondria-targeted compounds have been extensively evaluated in multiple laboratories using various *in vivo* and *in vitro* models of AD where some of them including a peptide, 6'-dimethyltyrosine-Lys-Phe-NH_2 (SS31), have been shown very efficacious in protecting against Af3-induced oxidative stress, synaptic loss, mitochondrial dysfunction, and abnormal calcium homeostasis [62]. Some of these compounds demonstrated promising results in clinical trials [211, 212]. Moreover, emerging data demonstrate that partial inhibition of OXPHOS with pharmacological inhibitors is beneficial in preventing obesity and type II diabetes, another risk factors contributing to AD [213–216], and promoting longevity in model organisms and in humans [217–220]. In particular, modulation of mitochondrial Complex I activity with small molecules was found efficacious in cognitive protection in multiple mouse models of AD [221] and in extending lifespan [222]. However, the details of molecular mechanism remain to be determined.

While supplementation with antioxidants so far appears to produce little modifying effect on AD development, non-pharmacological treatments and lifestyle interventions including exercise and caloric restriction have gained significant recent attention due to their overall positive effect on health and life span [223]. Specifically, grounded on a population-based perspective, the Alzheimer's Association has identified regular physical exercise as one of the strategies to reduce the risk of cognitive decline and the development of dementia [224]. Indeed, regular physical activity was associated with reduced oxidative stress, increased antioxidant capacity, increased anti-inflammatory effects, reduced levels of ceramides that are elevated in AD, improved Af3 clearance associated with the upregulating Af3 transporters, and induced neurogenesis [223, 225, 226]. The molecular mechanisms implicated in the beneficial effect of exercise are not fully understood. One of the explanations is based on the concept of mitohormesis, which suggests that an exposure to low continuous or higher intermittent sub-lethal doses of exercise-associated stress could lead to a mitochondrial adaptation by inducing changes in gene expression through exercise-sensitive transcription factors such as PGC1α, mtTFA, NF-KB, HIF-1, and p53. Downstream effects result in increase in mitochondrial biogenesis and antioxidant response. Potential signaling factors that mediate this mitochondria-nuclear communication may include ROS, calcium, mitochondrial unfolded protein response, mitochondrial metabolites, and mitokines [66, 227]. In addition to exercise, modulation of diet, especially caloric restriction, has been shown not only to extend lifespan, but also to protect against cognitive decline [228, 229]. However, a recent study demonstrated that meals rich in saturated fat and foods with a high glycemic index have differential effect in adults with and without cognitive impairment [230]. In

individuals without cognitive impairment, a consumption of high caloric food worsened cognitive performance, whereas consumption of high caloric food was beneficial in adults with cognitive impairment or the ApoE4 carriers. The authors also found that levels of Af3 in plasma were affected by meal type, suggesting a relationship between metabolic response and amyloid regulation. Therefore, a better understanding of the effect of diet modifications and exercise on metabolism, mitochondrial function and ROS production during different stages of disease progression is needed to develop safe and efficacious therapeutic strategies for AD.

CONCLUSIONS

Multiple lines of evidence provide strong support for the involvement of oxidative stress in the development of AD. At the same time, limited success of antioxidant therapies achieved to date emphasizes the need for better understanding of molecular mechanisms associated with different stages of AD development. Moreover, the dual role of ROS in essential neuroprotective cellular mechanisms versus detrimental effects of increased uncontrolled ROS production should be carefully considered while developing strategies to mitigate oxidative stress in neurodegenerative diseases.

ACKNOWLEDGMENTS

We thank Mr. Ivan Trushin for help with fig- ures. This work was supported by grant from NIEHS R01ES020715 (to ET). Its content is solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/16-1088r1).

REFERENCES

[1] (2015) Alzheimer's Disease International, https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf.

[2] Kandimalla R, Thirumala V, Reddy PH (2016) Is Alzheimer's disease a type 3 diabetes? A critical appraisal. *Biochim Biophys Acta*. doi: 10.1016/j.bbadis.2016.08.018

[3] Wang Y, Brinton RD (2016) Triad of risk for late onset Alzheimer's: Mitochondrial haplotype, APOE genotype and chromosomal sex. *Front Aging Neurosci* **8**, 232.

[4] Tramutola A, Lanzillotta C, Perluigi M, Butter- field DA (2016) Oxidative stress, protein modifica- tion and Alzheimer disease. *Brain Res Bull*. doi: 10.1016/j.brainresbull.2016.06.005

[5] Selkoe DJ (2008) Biochemistry and molecular biology of amyloid beta-protein and the mechanism of Alzheimer's disease. *Handb Clin Neurol* **89**, 245-260.

[6] LaFerla FM, Green KN, Oddo S (2007) Intracellular amyloid-beta in Alzheimer's disease. *Nat Rev Neurosci* **8**, 499-509.

[7] Selkoe DJ (2008) Soluble oligomers of the amyloid beta-protein impair synaptic plasticity and behavior. *Behav Brain Res* **192**, 106-113.

[8] Gyure KA, Durham R, Stewart WF, Smialek JE, Troncoso JC (2001) Intraneuronal abeta-amyloid precedes development of amyloid plaques in Down syndrome. *Arch Pathol Lab Med* **125**, 489-492.

[9] Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y, LaFerla FM (2003) Triple-transgenic model of Alzheimer's disease with plaques and tangles: Intracellular Abeta and synaptic dysfunction. *Neuron* **39**, 409-421.

[10] Knobloch M, Konietzko U, Krebs DC, Nitsch RM (2007) Intracellular Abeta and cognitive deficits precede beta-amyloid deposition in transgenic arcAbeta mice. *Neurobiol Aging* **28**, 1297-1306.

[11] Xu H, Greengard P, Gandy S (1995) Regulated formation of Golgi secretory vesicles containing Alzheimer beta-amyloid precursor protein. *J Biol Chem* **270**, 23243-23245.

[12] Kinoshita A, Fukumoto H, Shah T, Whelan CM, Irizarry MC, Hyman BT (2003) Demonstration by FRET of BACE interaction with the amyloid precursor protein at the cell surface and in early endosomes. *J Cell Sci* **116**, 3339-3346.

[13] Mizuguchi M, Ikeda K, Kim SU (1992) Differential distribution of cellular forms of beta-amyloid precursor protein in murine glial cell cultures. *Brain Res* **584**, 219-225.

[14] Omtri RS, Davidson MW, Arumugam B, Poduslo JF, Kandimalla KK (2012) Differences in the cellular uptake and intracellular itineraries of amyloid beta proteins 40 and 42: Ramifications for the Alzheimer's drug discovery. *Mol Pharm* **9**, 1887-1897.

[15] Cleary JP, Walsh DM, Hofmeister JJ, Shankar GM, Kuskowski MA, Selkoe DJ, Ashe KH (2005) Natural oligomers of the amyloid-beta protein specifically disrupt cognitive function. *Nat Neurosci* **8**, 79-84.

[16] Lai AY, McLaurin J (2010) Mechanisms of amyloid-beta peptide uptake by neurons: The role of lipid rafts and lipid raft-associated proteins. *Int J Alzheimers Dis* **2011**, 548380.

[17] Andreadis A, Brown WM, Kosik KS (1992) Structure and novel exons of the human tau gene. *Biochemistry* **31**, 10626-10633.

[18] Miller EC, Teravskis PJ, Dummer BW, Zhao X, Huganir RL, Liao D (2014) Tau phosphorylation and tau mislocalization mediate soluble Abeta oligomer-induced AMPA glutamate receptor signaling deficits. *Eur J Neurosci* **39**, 1214-1224.

[19] Selkoe DJ (2001) Alzheimer's disease results from the cerebral accumulation and cytotoxicity of amyloid beta-protein. *J Alzheimers Dis* **3**, 75-80.

[20] Jack CR Jr, Holtzman DM (2013) Biomarker modeling of Alzheimer's disease. *Neuron* **80**, 1347-1358.

[21] Crystal H, Dickson D, Fuld P, Masur D, Scott R, Mehler M, Masdeu J, Kawas C, Aronson M, Wolfson L (1988) Clinico-pathologic studies in dementia: Nondemented subjects with pathologically confirmed Alzheimer's disease. *Neurology* **38**, 1682-1687.

[22] Iacono D, Resnick SM, O'Brien R, Zonderman AB, An Y, Pletnikova O, Rudow G, Crain B, Troncoso JC (2014) Mild cognitive impairment and asymptomatic Alzheimer disease subjects: Equivalent beta-amyloid and tau loads with divergent cognitive outcomes. *J Neuropathol Exp Neurol* **73**, 295-304.

[23] Sepulcre J, Schultz AP, Sabuncu M, Gomez-Isla T, Chhatwal J, Becker A, Sperling R, Johnson KA (2016) In vivo tau, amyloid, and gray matter profiles in the aging brain. *J Neurosci* **36**, 7364-7374.

[24] Ossenkoppele R, Schonhaut DR, Scholl M, Lockhart SN, Ayakta N, Baker SL, O'Neil JP, Janabi M, Lazaris A, Cantwell A, Vogel J, Santos M, Miller ZA, Bettcher BM, Vossel KA, Kramer JH, Gorno-Tempini ML, Miller BL, Jagust WJ, Rabinovici GD (2016) Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. *Brain* **139**, 1551-1567.

[25] Wang L, Benzinger TL, Su Y, Christensen J, Friedrichsen K, Aldea P, McConathy J, Cairns NJ, Fagan AM, Morris JC, Ances BM (2016) Evaluation of tau imaging in staging Alzheimer disease and revealing interactions between beta-amyloid and tauopathy. *JAMA Neurol* **73**, 1070-1077.

[26] Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* **9**, 119-128.

[27] Holtzman DM, Morris JC, Goate AM (2011) Alzheimer's disease: The challenge of the second century. *Sci Transl Med* **3**, 77sr71.

[28] Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns NJ, Xie X, Blazey TM, Holtzman DM, Santacruz A, Buckles V, Oliver A, Moulder K, Aisen PS, Ghetti B, Klunk WE, McDade E, Martins RN, Masters CL, Mayeux R, Ringman JM, Rossor MN, Schofield PR, Sperling RA, Salloway S, Morris JC (2012) Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med* **367**, 795-804.

[29] Clark CM, Pontecorvo MJ, Beach TG, Bedell BJ, Coleman RE, Doraiswamy PM, Fleisher AS, Reiman EM, Sabbagh MN, Sadowsky CH, Schneider JA, Arora A, Carpenter AP, Flitter ML, Joshi AD, Krautkramer MJ, Lu M, Mintun MA, Skovronsky DM (2012) Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-beta plaques: A prospective cohort study. *Lancet Neurol* **11**, 669-678.

[30] Herrup K (2015) The case for rejecting the amyloid cascade hypothesis. *Nat Neurosci* **18**, 794-799.

[31] Castello MA, Jeppson JD, Soriano S (2014) Moving beyond anti-amyloid therapy for the prevention and treatment of Alzheimer's disease. *BMC Neurol* **14**, 169.

[32] Castellani RJ, Smith MA (2011) Compounding artefacts with uncertainty, and an amyloid cascade hypothesis that is 'too big to fail'. *J Pathol* **224**, 147-152.

[33] Swerdlow RH, Burns JM, Khan SM (2014) The Alzheimer's disease mitochondrial cascade hypothesis: Progress and perspectives. *Biochim Biophys Acta* **1842**, 1219-1231.

[34] Beal MF (1998) Mitochondrial dysfunction in neurodegenerative diseases. *Biochim Biophys Acta* **1366**, 211-223.

[35] Beal MF (2005) Oxidative damage as an early marker of Alzheimer's disease and mild cognitive impairment. *Neurobiol Aging* **26**, 585-586.

[36] Atamna H, Frey WH, 2nd (2007) Mechanisms of mitochondrial dysfunction and energy deficiency in Alzheimer's disease. *Mitochondrion* **7**, 297-310.

[37] Baloyannis SJ, Costa V, Michmizos D (2004) Mitochondrial alterations in Alzheimer's disease. *Am J Alzheimers Dis Other Demen* **19**, 89-93.

[38] Beal MF (2005) Mitochondria take center stage in aging and neurodegeneration. *Ann Neurol* **58**, 495-505.

[39] Calkins MJ, Manczak M, Mao P, Shirendeb U, Reddy PH (2011) Impaired mitochondrial biogenesis, defective axonal transport of mitochondria, abnormal mitochondrial dynamics and synaptic degeneration in a mouse model of Alzheimer's disease. *Hum Mol Genet* **20**, 4515-4529.

[40] Cardoso SM, Pereira CF, Moreira PI, Arduino DM, Esteves AR, Oliveira CR (2010) Mitochondrial control of autophagic lysosomal pathway in Alzheimer's disease. *Exp Neurol* **223**, 294-298.

[41] Cardoso SM, Santana I, Swerdlow RH, Oliveira CR (2004) Mitochondria dysfunction of Alzheimer's disease cybrids enhances Abeta toxicity. *J Neurochem* **89**, 1417-1426.

[42] Caspersen C, Wang N, Yao J, Sosunov A, Chen X, Lustbader JW, Xu HW, Stern D, McKhann G, Yan SD (2005) Mitochondrial Abeta: A potential focal point for neuronal metabolic dysfunction in Alzheimer's disease. *FASEB J* **19**, 2040-2041.

[43] Du H, Guo L, Yan S, Sosunov AA, McKhann GM, Yan SS (2010) Early deficits in synaptic mitochondria in an Alzheimer's disease mouse model. *Proc Natl Acad Sci U SA* **107**, 18670-18675.

[44] Eckert A, Hauptmann S, Scherping I, Rhein V, Muller-Spahn F, Gotz J, Muller WE (2008) Soluble beta-amyloid leads to mitochondrial defects in amyloid precursor protein and tau transgenic mice. *Neurodegener Dis* **5**, 157-159.

[45] Leuner K, Schutt T, Kurz C, Eckert SH, Schiller C, Occhipinti A, Mai S, Jendrach M, Eckert GP, Kruse SE, Palmiter RD, Brandt U, Drose S, Wittig I, Willem M, Haass C, Reichert AS, Muller WE (2012) Mitochondrion-derived reactive oxygen species lead to enhanced amyloid beta formation. *Antioxid Redox Signal* **16**, 1421-1433.

[46] Manczak M, Calkins MJ, Reddy PH (2011) Impaired mitochondrial dynamics and abnormal interaction of amyloid beta with mitochondrial protein Drp1 in neurons from patients with Alzheimer's disease: Implications for neuronal damage. *Hum Mol Genet* **20**, 2495-2509.

[47] Trushina E, McMurray CT (2007) Oxidative stress and mitochondrial dysfunction in neurodegenerative diseases. *Neuroscience* **145**, 1233-1248.

[48] Trushina E, Nemutlu E, Zhang S, Christensen T, Camp J, Mesa J, Siddiqui A, Tamura Y, Sesaki H, Wengenack TM, Dzeja PP, Poduslo JF (2012) Defects in mitochondrial dynamics and metabolomic signatures of evolving energetic stress in mouse models of familial Alzheimer's disease. *PLoS One* **7**, e32737.

[49] Zhu X, Perry G, Smith MA, Wang X (2013) Abnormal mitochondrial dynamics in the pathogenesis of Alzheimer's disease. *J Alzheimers Dis* **33**(Suppl 1), S253-S262.

[50] Kandimalla R, Reddy PH (2016) Multiple faces of dynamin-related protein 1 and its role in Alzheimer's disease pathogenesis. *Biochim Biophys Acta* **1862**, 814-828.

[51] Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, Saunders AM, Hardy J (2004) Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. *Proc Natl Acad Sci U S A* **101**, 284-289.

[52] Jagust WJ, Landau SM (2012) Apolipoprotein E, not fibrillar beta-amyloid, reduces cerebral glucose metabolism in normal aging. *J Neurosci* **32**, 18227-18233.

[53] Mosconi L, Pupi A, De Leon MJ (2008) Brain glucose hypometabolism and oxidative stress in preclinical Alzheimer's disease. *Ann N Y Acad Sci* **1147**, 180-195.

[54] Bubber P, Haroutunian V, Fisch G, Blass JP, Gibson GE (2005) Mitochondrial abnormalities in Alzheimer brain: Mechanistic implications. *Ann Neurol* **57**, 695-703.

[55] Blass JP (2000) The mitochondrial spiral. An adequate cause of dementia in the Alzheimer's syndrome. *Ann N Y Acad Sci* **924**, 170-183.

[56] Schmitt K, Grimm A, Kazmierczak A, Strosznajder JB, Gotz J, Eckert A (2012) Insights into mitochondrial dysfunction: Aging, amyloid-beta, and tau-A deleterious trio. *Antioxid Redox Signal* **16**, 1456-1466.

[57] Reddy PH (2011) Abnormal tau, mitochondrial dysfunction, impaired axonal transport of mitochondria, and synaptic deprivation in Alzheimer's disease. *Brain Res* **1415**, 136-148.

[58] Sultana R, Mecocci P, Mangialasche F, Cecchetti R, Baglioni M, Butterfield DA (2011) Increased protein and lipid oxidative damage in mitochondria isolated from lymphocytes from patients with Alzheimer's disease: Insights into the role of oxidative stress in Alzheimer's disease and initial investigations into a potential biomarker for this dementing disorder. *J Alzheimers Dis* **24**, 77-84.

[59] Caldwell CC, Yao J, Brinton RD (2015) Targeting the prodromal stage of Alzheimer's disease: Bioenergetic and mitochondrial opportunities. *Neurotherapeutics* **12**, 66-80.

[60] Yao J, Irwin RW, Zhao L, Nilsen J, Hamilton RT, Brinton RD (2009) Mitochondrial bioenergetic deficit precedes Alzheimer's pathology in female mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A* **106**, 14670-14675.

[61] Valla J, Yaari R, Wolf AB, Kusne Y, Beach TG, Roher AE, Corneveaux JJ, Huentelman MJ, Caselli RJ, Reiman EM (2010) Reduced posterior cingulate mitochondrial activity in expired young adult carriers of the APOE epsilon4 allele, the major late-onset Alzheimer's susceptibility gene. *J Alzheimers Dis* **22**, 307-313.

[62] Reddy PH, Tripathi R, Troung Q, Tirumala K, Reddy TP, Anekonda V, Shirendeb UP, Calkins MJ, Reddy AP, Mao P, Manczak M (2012) Abnormal mitochondrial dynamics and synaptic degeneration as early events in Alzheimer's disease: Implications to mitochondria-targeted antioxidant therapeutics. *Biochim Biophys Acta* **1822**, 639-649.

[63] Trushina E, Dutta T, Persson XM, Mielke MM, Petersen RC (2013) Identification of altered metabolic pathways in plasma and CSF in mild cognitive impairment and Alzheimer's disease using metabolomics. *PLoS One* **8**, e63644.

[64] Jones DP (2006) Redefining oxidative stress. *Antioxid Redox Signal* **8**, 1865-1879.

[65] Hauptmann N, Grimsby J, Shih JC, Cadenas E (1996) The metabolism of tyramine by monoamine oxidase A/B causes oxidative damage to mitochondrial DNA. *Arch Biochem Biophys* **335**, 295-304.

[66] Di Meo S, Reed TT, Venditti P, Victor VM (2016) Role of ROS and RNS sources in physiological and pathological conditions. *Oxid Med Cell Longe* **2016**, 1245049.

[67] Ray PD, Huang BW, Tsuji Y (2012) Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. *Cell Signal* **24**, 981-990.

[68] Holmstrom KM, Finkel T (2014) Cellular mechanisms and physiological consequences of redox-dependent signalling. *Nat Rev Mol Cell Biol* **15**, 411-421.

[69] Quinlan CL, Perevoshchikova IV, Hey-Mogensen M, Orr AL, Brand MD (2013) Sites of reactive oxygen species generation by mitochondria oxidizing different substrates. *Redox Biol* **1**, 304-312.

[70] Joshi G, Johnson JA (2012) The Nrf2-ARE pathway: A valuable therapeutic target for the treatment of neurodegenerative diseases. *Recent Pat CNS Drug Discov* **7**, 218-229.

[71] Kensler TW, Wakabayashi N, Biswal S (2007) Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. *Annu Rev Pharmacol Toxicol* **47**, 89-116.

[72] Denzer I, Munch G, Friedland K (2016) Modulation of mitochondrial dysfunction in neurodegenerative diseases via activation of nuclear factor erythroid-2-related factor 2 by food-derived compounds. *Pharmacol Res* **103**, 80-94.

[73] Patel M (2016) Targeting oxidative stress in central nervous system disorders. *Trends Pharmacol Sci* **37**, 768-778.

[74] Bhat AH, Dar KB, Anees S, Zargar MA, Masood A, Sofi MA, Ganie SA (2015) Oxidative stress, mitochondrial dysfunction and neurodegenerative diseases; a mechanistic insight. *Biomed Pharmacother* **74**, 101-110.

[75] Ramsey CP, Glass CA, Montgomery MB, Lindl KA, Ritson GP, Chia LA, Hamilton RL, Chu CT, Jordan-Sciutto KL (2007) Expression of Nrf2 in neurodegenerative diseases. *J Neuropathol Exp Neurol* **66**, 75-85.

[76] Tanji K, Maruyama A, Odagiri S, Mori F, Itoh K, Kakita A, Takahashi H, Wakabayashi K (2013) Keap1 is localized in neuronal and glial cytoplasmic inclusions in various neurodegenerative diseases. *J Neuropathol Exp Neurol* **72**, 18-28.

[77] Schipper HM, Bennett DA, Liberman A, Bienias JL, Schneider JA, Kelly J, Arvanitakis Z (2006) Glial heme oxygenase-1 expression in Alzheimer disease and mild cognitive impairment. *Neurobiol Aging* **27**, 252-261.

[78] Kanninen K, Malm TM, Jyrkkanen HK, Goldsteins G, Keksa-Goldsteine V, Tanila H, Yamamoto M, Ylä-Herttuala S, Levonen AL, Koistinaho J (2008) Nuclear factor erythroid 2-related factor 2 protects against beta amyloid. *Mol Cell Neurosci* **39**, 302-313.

[79] Kim TS, Pae CU, Yoon SJ, Jang WY, Lee NJ, Kim JJ, Lee SJ, Lee C, Paik IH, Lee CU (2006) Decreased plasma antioxidants in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* **21**, 344-348.

[80] Uttara B, Singh AV, Zamboni P, Mahajan RT (2009) Oxidative stress and neurodegenerative diseases: A review of upstream and downstream antioxidant therapeutic options. *Curr Neuropharmacol* **7**, 65-74.

[81] Smith MA, Rudnicka-Nawrot M, Richey PL, Praprotnik D, Mulvihill P, Miller CA, Sayre LM, Perry G (1995) Carbonyl-related posttranslational modification of neurofilament protein in the neurofibrillary pathology of Alzheimer's disease. *J Neurochem* **64**, 2660-2666.

[82] Butterfield DA, Di Domenico F, Barone E (2014) Elevated risk of type 2 diabetes for development of Alzheimer disease: A key role for oxidative stress in brain. *Biochim Biophys Acta* **1842**, 1693-1706.

[83] Kosenko EA, Solomadin IN, Tikhonova LA, Reddy VP, Aliev G, Kaminsky YG (2014) Pathogenesis of Alzheimer disease: Role of oxidative stress, amyloid-beta peptides, systemic ammonia and erythrocyte energy metabolism. *CNS Neurol Disord Drug Targets* **13**, 112-119.

[84] Castellani RJ, Moreira PI, Perry G, Zhu X (2012) The role of iron as a mediator of oxidative stress in Alzheimer disease. *Biofactors* **38**, 133-138.

[85] Zhu X, Raina AK, Lee HG, Chao M, Nunomura A, Tabaton M, Petersen RB, Perry G, Smith MA (2003) Oxidative stress and neuronal adaptation in Alzheimer disease: The role of SAPK pathways. *Antioxid Redox Signal* **5**, 571-576.

[86] Markesbery WR (1999) The role of oxidative stress in Alzheimer disease. *Arch Neurol* **56**, 1449-1452.

[87] Pratico D (2008) Oxidative stress hypothesis in Alzheimer's disease: A reappraisal. *Trends Pharmacol Sci* **29**, 609-615.

[88] Schippling S, Kontush A, Arlt S, Buhmann C, Sturenburg HJ, Mann U, Muller-Thomsen T, Beisiegel U (2000) Increased lipoprotein oxidation in Alzheimer's disease. *Free Radic Biol Med* **28**, 351-360.

[89] Smith MA, Kutty RK, Richey PL, Yan SD, Stern D, Chader GJ, Wiggert B, Petersen RB, Perry G (1994) Heme oxygenase-1 is associated with the neurofibrillary pathology of Alzheimer's disease. *Am J Pathol* **145**, 42-47.

[90] Ramassamy C, Krzywkowski P, Averill D, Lussier-Cacan S, Theroux L, Christen Y, Davignon J, Poirier J (2001) Impact of apoE deficiency on oxidative insults and antioxidant levels in the brain. *Brain Res Mol Brain Res* **86**, 76-83.

[91] Picklo MJ, Montine TJ, Amarnath V, Neely MD (2002) Carbonyl toxicology and Alzheimer's disease. *Toxicol Appl Pharmacol* **184**, 187-197.

[92] Bassett CN, Montine TJ (2003) Lipoproteins and lipid peroxidation in Alzheimer's disease. *J Nutr Health Aging* **7**, 24-29.

[93] Mecocci P, Beal MF, Cecchetti R, Polidori MC, Cherubini A, Chionne F, Avellini L, Romano G, Senin U (1997) Mitochondrial membrane fluidity and oxidative damage to mitochondrial DNA in aged and AD human brain. *Mol Chem Neuropathol* **31**, 53-64.

[94] Lovell MA, Markesbery WR (2007) Oxidative DNA damage in mild cognitive impairment and late-stage Alzheimer's disease. *Nucleic Acids Res* **35**, 7497-7504.

[95] Lovell MA, Markesbery WR (2008) Oxidatively modified RNA in mild cognitive impairment. *Neurobiol Dis* **29**, 169-175.

[96] Bradley-Whitman MA, Timmons MD, Beckett TL, Murphy MP, Lynn BC, Lovell MA (2014) Nucleic acid oxidation: An early feature of Alzheimer's disease. *J Neurochem* **128**, 294-304.

[97] Migliore L, Fontana I, Trippi F, Colognato R, Coppede F, Tognoni G, Nucciarone B, Siciliano G (2005) Oxidative DNA damage in peripheral leukocytes of mild cognitive impairment and AD patients. *Neurobiol Aging* **26**, 567-573.

[98] Greenough MA, Camakaris J, Bush AI (2013) Metal dyshomeostasis and oxidative stress in Alzheimer's disease. *Neurochem Int* **62**, 540-555.

[99] Wang P, Wang ZY (2016) Metal ions influx is a double edged sword for the pathogenesis of Alzheimer's disease. *Ageing Res Rev*. doi: 10.1016/j.arr.2016.10.003

[100] Liu G, Huang W, Moir RD, Vanderburg CR, Lai B, Peng Z, Tanzi RE, Rogers JT, Huang X (2006) Metal exposure and Alzheimer's pathogenesis. *J Struct Biol* **155**, 45-51.

[101] Danscher G, Jensen KB, Frederickson CJ, Kemp K, Andreasen A, Juhl S, Stoltenberg M, Ravid R (1997) Increased amount of zinc in the hippocampus and amygdala of Alzheimer's diseased brains: A proton-induced X-ray emission spectroscopic analysis of cryostat sections from autopsy material. *J Neurosci Methods* **76**, 53-59.

[102] Friedlich AL, Lee JY, van Groen T, Cherny RA, Volitakis I, Cole TB, Palmiter RD, Koh JY, Bush AI (2004) Neuronal zinc exchange with the blood vessel wall promotes cerebral amyloid angiopathy in an animal model of Alzheimer's disease. *J Neurosci* **24**, 3453-3459.

[103] Lee JY, Cole TB, Palmiter RD, Suh SW, Koh JY (2002) Contribution by synaptic zinc to the gender-disparate plaque formation in human Swedish mutant APP transgenic mice. *Proc Natl Acad Sci USA* **99**, 7705-7710.

[104] Lee JY, Mook-Jung I, Koh JY (1999) Histochemically reactive zinc in plaques of the Swedish mutant beta-amyloid precursor protein transgenic mice. *J Neurosci* **19**, RC10.

[105] Lovell MA, Robertson JD, Teesdale WJ, Campbell JL, Markesbery WR (1998) Copper, iron and zinc in Alzheimer's disease senile plaques. *J Neurol Sci* **158**, 47-52.

[106] Miller LM, Wang Q, Telivala TP, Smith RJ, Lanzirotti A, Miklossy J (2006) Synchrotron-based infrared and X-ray imaging shows focalized accumulation of Cu and Zn co-localized with beta-amyloid deposits in Alzheimer's disease. *J Struct Biol* **155**, 30-37.

[107] Stoltenberg M, Bush AI, Bach G, Smidt K, Larsen A, Rungby J, Lund S, Doering P, Danscher G (2007) Amyloid plaques arise from zinc-enriched cortical layers in APP/PS1 transgenic mice and are paradoxically enlarged with dietary zinc deficiency. *Neuroscience* **150**, 357-369.

[108] Suh SW, Jensen KB, Jensen MS, Silva DS, Kesslak PJ, Danscher G, Frederickson CJ (2000) Histochemically-reactive zinc in amyloid plaques, angiopathy, and degenerating neurons of Alzheimer's diseased brains. *Brain Res* **852**, 274-278.

[109] Boom A, Pochet R, Authelet M, Pradier L, Borghgraef P, Van Leuven F, Heizmann CW, Brion JP (2004) Astrocytic calcium/zinc binding protein S100A6 over expression in Alzheimer's disease and in PS1/APP transgenic mice models. *Biochim Biophys Acta* **1742**, 161-168.

[110] Heizmann CW, Cox JA (1998) New perspectives on S100 proteins: A multi-functional Ca(2+)-, Zn(2+)- and Cu(2+)-binding protein family. *Biometals* **11**, 383-397.

[111] Barnham KJ, Bush AI (2014) Biological metals and metal-targeting compounds in major neurodegenerative diseases. *Chem Soc Rev* **43**, 6727-6749.

[112] Lammich S, Kojro E, Postina R, Gilbert S, Pfeiffer R, Jasionowski M, Haass C, Fahrenholz F (1999) Constitutive and regulated alpha-secretase cleavage of Alzheimer's amyloid precursor protein by a disintegrin metalloprotease. *Proc Natl Acad Sci USA* **96**, 3922-3927.

[113] Bush AI, Pettingell WH, Multhaup G, d Paradis M, Vonsattel JP, Gusella JF, Beyreuther K, Masters CL, Tanzi RE (1994) Rapid induction of Alzheimer A beta amyloid formation by zinc. *Science* **265**, 1464-1467.

[114] Tougu V, Karafin A, Palumaa P (2008) Binding of zinc(II) and copper(II) to the full-length Alzheimer's amyloid-beta peptide. *J Neurochem* **104**, 1249-1259.

[115] Mantyh PW, Ghilardi JR, Rogers S, DeMaster E, Allen CJ, Stimson ER, Maggio JE (1993) Aluminum, iron, and zinc ions promote aggregation of physiological concentrations of beta-amyloid peptide. *J Neurochem* **61**, 1171-1174.

[116] Sayre LM, Perry G, Harris PL, Liu Y, Schubert KA, Smith MA (2000) In situ oxidative catalysis by neurofibrillary tangles and senile plaques in Alzheimer's disease:

A central role for bound transition metals. *J Neurochem* **74**, 270-279.

[117] Boom A, Authelet M, Dedecker R, Frederick C, Van Heurck R, Daubie V, Leroy K, Pochet R, Brion JP (2009) Bimodal modulation of tau protein phosphorylation and conformation by extracellular Zn2+ in human-tau transfected cells. *Biochim Biophys Acta* **1793**, 1058-1067.

[118] Stohs SJ, Bagchi D (1995) Oxidative mechanisms in the toxicity of metal ions. *Free Radic Biol Med* **18**, 321-336.

[119] Huang X, Atwood CS, Hartshorn MA, Multhaup G, Goldstein LE, Scarpa RC, Cuajungco MP, Gray DN, Lim J, Moir RD, Tanzi RE, Bush AI (1999) The A beta peptide of Alzheimer's disease directly produces hydrogen peroxide through metal ion reduction. *Biochemistry* **38**, 7609-7616.

[120] Adlard PA, Cherny RA, Finkelstein DI, Gautier E, Robb E, Cortes M, Volitakis I, Liu X, Smith JP, Perez K, Laughton K, Li QX, Charman SA, Nicolazzo JA, Wilkins S, Deleva K, Lynch T, Kok G, Ritchie CW, Tanzi RE, Cappai R, Masters CL, Barnham KJ, Bush AI (2008) Rapid restoration of cognition in Alzheimer's transgenic mice with 8-hydroxy quinoline analogs is associated with decreased interstitial Abeta. *Neuron* **59**, 43-55.

[121] Cherny RA, Atwood CS, Xilinas ME, Gray DN, Jones WD, McLean CA, Barnham KJ, Volitakis I, Fraser FW, Kim Y, Huang X, Goldstein LE, Moir RD, Lim JT, Beyreuther K, Zheng H, Tanzi RE, Masters CL, Bush AI (2001) Treatment with a copper-zinc chelator markedly and rapidly inhibits beta-amyloid accumulation in Alzheimer's disease transgenic mice. *Neuron* **30**, 665-676.

[122] Opazo C, Barria MI, Ruiz FH, Inestrosa NC (2003) Copper reduction by copper binding proteins and its relation to neurodegenerative diseases. *Biometals* **16**, 91-98.

[123] Cristovao JS, Santos R, Gomes CM (2016) Metals and Neuronal Metal Binding Proteins Implicated in Alzheimer's Disease. *Oxid Med Cell Longe* **2016**, 9812178.

[124] Nakajima K, Kohsaka S (2001) Microglia: Activation and their significance in the central nervous system. *J Biochem* **130**, 169-175.

[125] Gibson GE, Karuppagounder SS, Shi Q (2008) Oxidant-induced changes in mitochondria and calcium dynamics in the pathophysiology of Alzheimer's disease. *Ann N Y Acad Sci* **1147**, 221-232.

[126] Manczak M, Anekonda TS, Henson E, Park BS, Quinn J, Reddy PH (2006) Mitochondria are a direct site of Abeta accumulation in Alzheimer's disease neurons: Implications for free radical generation and oxidative damage in disease progression. *Hum Mol Genet* **15**, 1437-1449.

[127] Mattson MP, Cutler RG, Jo DG (2005) Alzheimer peptides perturb lipid-regulating enzymes. *Nat Cell Biol* **7**, 1045-1047.

[128] Lee JT, Xu J, Lee JM, Ku G, Han X, Yang DI, Chen S, Hsu CY (2004) Amyloid-beta peptide induces oligodendrocyte death by activating the neutral sphingomyelinase-ceramide pathway. *J Cell Biol* **164**, 123-131.

[129] Grimm MO, Grimm HS, Patzold AJ, Zinser EG, Halonen R, Duering M, Tschape JA, De Strooper B, Muller U, Shen J, Hartmann T (2005) Regulation of cholesterol and sphingomyelin metabolism by amyloid-beta and presenilin. *Nat Cell Biol* **7**, 1118-1123.

[130] Cutler RG, Kelly J, Storie K, Pedersen WA, Tammara A, Hatanpaa K, Troncoso JC, Mattson MP (2004) Involvement of oxidative stress-induced abnormalities in ceramide and cholesterol metabolism in brain aging and Alzheimer's disease. *Proc Natl Acad Sci U S A* **101**, 2070-2075.

[131] Chalfant CE, Kishikawa K, Mumby MC, Kamibayashi C, Bielawska A, Hannun YA (1999) Long chain ceramides activate protein phosphatase-1 and protein phosphatase-2A. Activation is stereospecific and regulated by phosphatidic acid. *J Biol Chem* **274**, 20313-20317.

[132] Haughey NJ, Bandaru VV, Bae M, Mattson MP (2010) Roles for dysfunctional sphingolipid metabolism in Alzheimer's disease neuropathogenesis. *Biochim Biophys Acta* **1801**, 878-886.

[133] Blass JP, Baker AC, Ko L, Black RS (1990) Induction of Alzheimer antigens by an uncoupler of oxidative phosphorylation. *Arch Neurol* **47**, 864-869.

[134] Szabados T, Dul C, Majtenyi K, Hargitai J, Penzes Z, Urbanics R (2004) A chronic Alzheimer's model evoked by mitochondrial poison sodium azide for pharmacological investigations. *Behav Brain Res* **154**, 31-40.

[135] Ichimura H, Parthasarathi K, Quadri S, Issekutz AC, Bhattacharya J (2003) Mechano-oxidative coupling by mitochondria induces proinflammatory responses in lung venular capillaries. *J Clin Invest* **111**, 691-699.

[136] Colell A, Fernandez A, Fernandez-Checa JC (2009) Mitochondria, cholesterol and amyloid beta peptide: A dangerous trio in Alzheimer disease. *J Bioenerg Biomembr* **41**, 417-423.

[137] Rosales-Corral SA, Lopez-Armas G, Cruz-Ramos J, Melnikov VG, Tan DX, Manchester LC, Munoz R, Reiter RJ (2012) Alterations in lipid levels of mitochondrial membranes induced by amyloid-beta: A protective role of melatonin. *Int J Alzheimers Dis* **2012**, 459806.

[138] Mondragon-Rodriguez S, Perry G, Zhu X, Moreira PI, Acevedo-Aquino MC, Williams S (2013) Phosphorylation of tau protein as the link between oxidative stress, mitochondrial dysfunction, and connectivity failure: Implications for Alzheimer's disease. *Oxid Med Cell Longe* **2013**, 940603.

[139] Vlassenko AG, Vaishnavi SN, Couture L, Sacco D, Shannon BJ, Mach RH, Morris JC, Raichle ME, Mintun MA (2010) Spatial correlation between brain aerobic glycolysis and amyloid-beta (Abeta) deposition. *Proc Natl Acad Sci USA* **107**, 17763-17767.

[140] Onyango IG, Ahn JY, Tuttle JB, Bennett JP Jr, Swerdlow RH (2010) Nerve growth factor attenuates oxidant-induced beta-amyloid neurotoxicity in sporadic Alzheimer's disease cybrids. *J Neurochem* **114**, 1605-1618.

[141] Khan SM, Cassarino DS, Abramova NN, Keeney PM, Borland MK, Trimmer PA, Krebs CT, Bennett JC, Parks JK, Swerdlow RH, Parker WD Jr, Bennett JP Jr (2000) Alzheimer's disease cybrids replicate beta-amyloid abnormalities through cell death pathways. *Ann Neurol* **48**, 148-155.

[142] Gasparini L, Racchi M, Benussi L, Curti D, Binetti G, Bianchetti A, Trabucchi M, Govoni S (1997) Effect of energy shortage and oxidative stress on amyloid precursor protein metabolism in COS cells. *Neurosci Lett* **231**, 113-117.

[143] Gabuzda D, Busciglio J, Chen LB, Matsudaira P, Yankner BA (1994) Inhibition of energy metabolism alters the processing of amyloid precursor protein and induces a potentially amyloidogenic derivative. *J Biol Chem* **269**, 13623-13628.

[144] Webster MT, Pearce BR, Bowen DM, Francis PT (1998) The effects of perturbed energy metabolism on the processing of amyloid precursor protein in PC12 cells. *J Neural Transm (Vienna)* **105**, 839-853.

[145] Henriques AG, Domingues SC, Fardilha M, da Cruz e Silva EF, da Cruz e Silva OA (2005) Sodium azide and 2-deoxy-D-glucose-induced cellular stress affects phosphorylation-dependent AbetaPP processing. *J Alzheimers Dis* **7**, 201-212; discussion 255-262.

[146] Szule JA, Jung JH, McMahan UJ (2015) The structure and function of 'active zone material' at synapses. *Philos Trans R Soc Lond B Biol Sci* **370**, 1672.

[147] Malenka RC, Bear MF (2004) LTP and LTD: An embarrassment of riches. *Neuron* **44**, 5-21.

[148] Neves G, Cooke SF, Bliss TV (2008) Synaptic plasticity, memory and the hippocampus: A neural network approach to causality. *Nat Rev Neurosci* **9**, 65-75.

[149] Mattson MP, Magnus T (2006) Ageing and neuronal vulnerability. *Nat Rev Neurosci* **7**, 278-294.

[150] Jang SS, Chung HJ (2016) Emerging link between Alzheimer's disease and homeostatic synaptic plasticity. *Neural Plas* **2016**, 7969272.

[151] DeKosky ST, Scheff SW (1990) Synapse loss in frontal cortex biopsies in Alzheimer's disease: Correlation with cognitive severity. *Ann Neurol* **27**, 457-464.

[152] Hamos JE, DeGennaro LJ, Drachman DA (1989) Synaptic loss in Alzheimer's disease and other dementias. *Neurology* **39**, 355-361.

[153] Robinson JL, Molina-Porcel L, Corrada MM, Raible K, Lee EB, Lee VM, Kawas CH, Trojanowski JQ (2014) Perforant path synaptic loss correlates with cognitive impairment and Alzheimer's disease in the oldest-old. *Brain* **137**, 2578-2587.

[154] Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R (1991) Physical basis of cognitive alterations in Alzheimer's disease: Synapse loss is the major correlate of cognitive impairment. *Ann Neurol* **30**, 572-580.

[155] Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT (2011) Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med* **1**, a006189.

[156] Cooper LN, Bear MF (2012) The BCM theory of synapse modification at 30: Interaction of theory with experiment. *Nat Rev Neurosci* **13**, 798-810.

[157] Spires-Jones TL, Hyman BT (2014) The intersection of amyloid beta and tau at synapses in Alzheimer's disease. *Neuron* **82**, 756-771.

[158] Kamat PK, Kalani A, Rai S, Swarnkar S, Tota S, Nath C, Tyagi N (2016) Mechanism of oxidative stress and synapse dysfunction in the pathogenesis of Alzheimer's disease: Understanding the therapeutics strategies. *Mol Neurobiol* **53**, 648-661.

[159] Reddy PH, Beal MF (2008) Amyloid beta, mitochondrial dysfunction and synaptic damage: Implications for cognitive decline in aging and Alzheimer's disease. *Trends Mol Med* **14**, 45-53.

[160] Newcomer JW, Farber NB, Olney JW (2000) NMDA receptor function, memory, and brain aging. *Dialogues Clin Neurosci* **2**, 219-232.

[161] Frankland PW, Bontempi B (2005) The organization of recent and remote memories. *Nat Rev Neurosci* **6**, 119-130.

[162] Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, Nairn AC, Salter MW, Lombroso PJ, Gouras GK, Greengard P (2005) Regulation of NMDA receptor trafficking by amyloid-beta. *Nat Neurosci* **8**, 1051-1058.

[163] Bezprozvanny I, Mattson MP (2008) Neuronal calcium mishandling and the pathogenesis of Alzheimer's disease. *Trends Neurosci* **31**, 454-463.

[164] Parsons MP, Raymond LA (2014) Extrasynaptic NMDA receptor involvement in central nervous system disorders. *Neuron* **82**, 279-293.

[165] Lipton SA (2006) Paradigm shift in neuroprotection by NMDA receptor blockade: Memantine and beyond. *Nat Rev Drug Discov* **5**, 160-170.

[166] Hsieh H, Boehm J, Sato C, Iwatsubo T, Tomita T, Sisodia S, Malinow R (2006) AMPAR removal underlies Abeta-induced synaptic depression and dendritic spine loss. *Neuron* **52**, 831-843.

[167] Li Y, Sun H, Chen Z, Xu H, Bu G, Zheng H (2016) Implications of GABAergic neurotransmission in Alzheimer's disease. *Front Aging Neurosci* **8**, 31.

[168] Schliebs R, Arendt T (2011) The cholinergic system in aging and neuronal degeneration. *Behav Brain Res* **221**, 555-563.

[169] Campos C, Rocha NB, Vieira RT, Rocha SA, Telles-Correia D, Paes F, Yuan T, Nardi AE, Arias-Carrion O, Machado S, Caixeta L (2016) Treatment of cognitive deficits in Alzheimer's disease: A psychopharmacological review. *Psychiatr Danub* **28**, 2-12.

[170] Ellis B, Hye A, Snowden SG (2015) Metabolic modifications in human biofluids suggest the involvement of sphingolipid, antioxidant, and glutamate metabolism in Alzheimer's disease pathogenesis. *J Alzheimers Dis* **46**, 313-327.

[171] Trushina E, Mielke MM (2013) Recent advances in the application of metabolomics to Alzheimer's Disease. *Biochim Biophys Acta* **1842**, 1232-1239.

[172] De Felice FG, Velasco PT, Lambert MP, Viola K, Fernandez SJ, Ferreira ST, Klein WL (2007) Abeta oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine. *J Biol Chem* **282**, 11590-11601.

[173] Rai S, Kamat PK, Nath C, Shukla R (2013) A study on neuroinflammation and NMDA receptor function in STZ (ICV) induced memory impaired rats. *J Neuroimmunol* **254**, 1-9.

[174] Kamat PK, Rai S, Swarnkar S, Shukla R, Ali S, Najmi AK, Nath C (2013) Okadaic acid-induced Tau phosphorylation in rat brain: Role of NMDA receptor. *Neuroscience* **238**, 97-113.

[175] Morris G, Walder K, Puri BK, Berk M, Maes M (2016) The deleterious effects of oxidative and nitrosative stress on palmitoylation, membrane lipid rafts and lipid-based cellular signalling: New drug targets in neuroimmune disorders. *Mol Neurobiol* **53**, 4638-4658.

[176] Han X (2010) Multi-dimensional mass spectrometry-based shotgun lipidomics and the altered lipids at the mild cognitive impairment stage of Alzheimer's disease. *Biochim Biophys Acta* **1801**, 774-783.

[177] Han X, Rozen S, Boyle SH, Hellegers C, Cheng H, Burke JR, Welsh-Bohmer KA, Doraiswamy PM, Kaddurah-Daouk R (2011) Metabolomics in early Alzheimer's disease: Identification of altered plasma sphingolipidome using shotgun lipidomics. *PLoS One* **6**, e21643.

[178] Schneider LS, Sano M (2009) Current Alzheimer's disease clinical trials: Methods and placebo outcomes. *Alzheimers Dement* **5**, 388-397.

[179] Cummings J, Aisen PS, DuBois B, Frolich L, Jack CR Jr, Jones RW, Morris JC, Raskin J, Dowsett SA, Scheltens

P (2016) Drug development in Alzheimer's disease: The path to 2025. *Alzheimers Res Ther* **8**, 39.

[180] Padurariu M, Ciobica A, Lefter R, Serban IL, Stefanescu C, Chirita R (2013) The oxidative stress hypothesis in Alzheimer's disease. *Psychiatr Danub* **25**, 401-409.

[181] Sancheti H, Kanamori K, Patil I, Diaz Brinton R, Ross BD, Cadenas E (2014) Reversal of metabolic deficits by lipoic acid in a triple transgenic mouse model of Alzheimer's disease: A 13C NMR study. *J Cereb Blood Flow Metab* **34**, 288-296.

[182] Quinn JF, Bussiere JR, Hammond RS, Montine TJ, Henson E, Jones RE, Stackman RW Jr (2007) Chronic dietary alpha-lipoic acid reduces deficits in hippocampal memory of aged Tg2576 mice. *Neurobiol Aging* **28**, 213-225.

[183] Rajasekar N, Dwivedi S, Tota SK, Kamat PK, Hanif K, Nath C, Shukla R (2013) Neuroprotective effect of curcumin on okadaic acid induced memory impairment in mice. *Eur J Pharmacol* **715**, 381-394.

[184] Zhou X, Li Y, Shi X, Ma C (2016) An overview on therapeutics attenuating amyloid beta level in Alzheimer's disease: Targeting neurotransmission, inflammation, oxidative stress and enhanced cholesterol levels. *Am J Transl Res* **8**, 246-269.

[185] Kang JH, Cook N, Manson J, Buring JE, Grodstein F (2006) A randomized trial of vitamin E supplementation and cognitive function in women. *Arch Intern Med* **166**, 2462-2468.

[186] Kang JH, Cook NR, Manson JE, Buring JE, Albert CM, Grodstein F (2009) Vitamin E, vitamin C, beta carotene, and cognitive function among women with or at risk of cardiovascular disease: The Women's Antioxidant and Cardiovascular Study. *Circulation* **119**, 2772-2780.

[187] Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, Galasko D, Jin S, Kaye J, Levey A, Pfeiffer E, Sano M, van Dyck CH, Thal LJ, Alzheimer's Disease Cooperative Study Group (2005) Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* **352**, 2379-2388.

[188] Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, Woodbury P, Growdon J, Cotman CW, Pfeiffer E, Schneider LS, Thal LJ (1997) A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *N Engl J Med* **336**, 1216-1222.

[189] Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M, Love S, Schellenberg GD, McCarten JR, Malphurs J, Prieto S, Chen P, Loreck DJ, Trapp G, Bakshi RS, Mintzer JE, Heidebrink JL, Vidal-Cardona A, Arroyo LM, Cruz AR, Zachariah S, Kowall NW, Chopra MP, Craft S, Thielke S, Turvey CL, Woodman C, Monnell KA, Gordon K, Tomaska J, Segal Y, Peduzzi PN, Guarino PD (2014) Effect of vitamin E and memantine on functional decline in Alzheimer disease: The TEAM-AD VA cooperative randomized trial. *JAMA* **311**, 33-44.

[190] Miller ER, 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E (2005) Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* **142**, 37-46.

[191] Arlt S, Muller-Thomsen T, Beisiegel U, Kontush A (2012) Effect of one-year vitamin C- and E-supplementation on cerebrospinal fluid oxidation parameters and clinical course in Alzheimer's disease. *Neurochem Res* **37**, 2706-2714.

[192] Galasko DR, Peskind E, Clark CM, Quinn JF, Ringman JM, Jicha GA, Cotman C, Cottrell B, Montine TJ, Thomas RG, Aisen P, Alzheimer's Disease Cooperative Study (2012) Antioxidants for Alzheimer disease: A randomized clinical trial with cerebrospinal fluid biomarker measures. *Arch Neurol* **69**, 836-841.

[193] Ringman JM, Frautschy SA, Teng E, Begum AN, Bardens J, Beigi M, Gylys KH, Badmaev V, Heath DD, Apostolova LG, Porter V, Vanek Z, Marshall GA, Hellemann G, Sugar C, Masterman DL, Montine TJ, Cummings JL, Cole GM (2012) Oral curcumin for Alzheimer's disease: Tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study. *Alzheimers Res Ther* **4**, 43.

[194] Wojtunik-Kulesza KA, Oniszczuk A, Oniszczuk T, Waksmundzka-Hajnos M (2016) The influence of common free radicals and antioxidants on development of Alzheimer's Disease. *Biomed Pharmacother* **78**, 39-49.

[195] Mecocci P, Polidori MC (2012) Antioxidant clinical trials in mild cognitive impairment and Alzheimer's disease. *Biochim Biophys Acta* **1822**, 631-638.

[196] Tolonen M, Halme M, Sarna S (1985) Vitamin E and selenium supplementation in geriatric patients: A double-blind preliminary clinical trial. *Biol Trace Elem Res* **7**, 161-168.

[197] Kryscio RJ, Abner EL, Schmitt FA, Goodman PJ, Mendiondo M, Caban-Holt A, Dennis BC, Mathews M, Klein EA, Crowley JJ, Investigators SELECT (2013) A randomized controlled Alzheimer's disease prevention trial's evolution into an exposure trial: The PREADViSE Trial. *J Nutr Health Aging* **17**, 72-75.

[198] Dias KS, Viegas C, Jr (2014) Multi-target directed drugs: A modern approach for design of new drugs for the treatment of Alzheimer's disease. *Curr Neuropharmacol* **12**, 239-255.

[199] Remington R, Bechtel C, Larsen D, Samar A, Page R, Morrell C, Shea TB (2016) Maintenance of cognitive performance and mood for individuals with Alzheimer's disease following consumption of a nutraceutical formulation: A one-year, open-label study. *J Alzheimers Dis* **51**, 991-995.

[200] Chan A, Remington R, Kotyla E, Lepore A, Zemianek J, Shea TB (2010) A vitamin/nutriceutical formulation improves memory and cognitive performance in community-dwelling adults without dementia. *J Nutr Health Aging* **14**, 224-230.

[201] Banerjee P, Maity S, Das T, Mazumder S (2011) A double-blind randomized placebo-controlled clinical study to evaluate the efficacy and safety of a polyherbal formulation in geriatric age group: A phase IV clinical report. *J Ethnopharmacol* **134**, 429-433.

[202] Meng TC, Fukada T, Tonks NK (2002) Reversible oxidation and inactivation of protein tyrosine phosphatases *in vivo*. *Mol Cell* **9**, 387-399.

[203] Kwon J, Lee SR, Yang KS, Ahn Y, Kim YJ, Stadtman ER, Rhee SG (2004) Reversible oxidation and inactivation of the tumor suppressor PTEN in cells stimulated with peptide growth factors. *Proc Natl Acad Sci U S A* **101**, 16419-16424.

[204] Edgar RS, Green EW, Zhao Y, van Ooijen G, Olmedo M, Qin X, Xu Y, Pan M, Valekunja UK, Feeney KA, Maywood ES, Hastings MH, Baliga NS, Merrow M, Millar AJ, Johnson CH, Kyriacou CP, O'Neill JS, Reddy AB (2012) Peroxiredoxins are conserved markers of circadian rhythms. *Nature* **485**, 459-464.

[205] Ha EM, Oh CT, Bae YS, Lee WJ (2005) A direct role for dual oxidase in Drosophila gut immunity. *Science* **310**, 847-850.

[206] Mathers J, Fraser JA, McMahon M, Saunders RD, Hayes JD, McLellan LI (2004) Antioxidant and cytoprotective responses to redox stress. *Biochem Soc Symp*, 157-176.

[207] Mattson MP (2008) Hormesis defined. *Ageing Res Rev* **7**, 1-7.

[208] Ristow M (2014) Unraveling the truth about antioxidants: Mitohormesis explains ROS-induced health benefits. *Nat Med* **20**, 709-711.

[209] Schmeisser S, Priebe S, Groth M, Monajembashi S, Hemmerich P, Guthke R, Platzer M, Ristow M (2013) Neuronal ROS signaling rather than AMPK/sirtuin-mediated energy sensing links dietary restriction to lifespan extension. *Mol Metab* **2**, 92-102.

[210] Droge W (2002) Free radicals in the physiological control of cell function. *Physiol Rev* **82**, 47-95.

[211] Kumar A, Singh A (2015) A review on mitochondrial restorative mechanism of antioxidants in Alzheimer's disease and other neurological conditions. *Front Pharmaco* **6**, 206.

[212] Feniouk BA, Skulachev VP (2016) Cellular and molecular mechanisms of action of mitochondria-targeted antioxidants. *Curr Aging Sci*. doi: 10.2174-1874609809666160921113706

[213] Pospisilik JA, Knauf C, Joza N, Benit P, Orthofer M, Cani PD, Ebersberger I, Nakashima T, Sarao R, Neely G, Esterbauer H, Kozlov A, Kahn CR, Kroemer G, Rustin P, Burcelin R, Penninger JM (2007) Targeted deletion of AIF decreases mitochondrial oxidative phosphorylation and protects from obesity and diabetes. *Cell* **131**, 476-491.

[214] Wredenberg A, Freyer C, Sandstrom ME, Katz A, Wibom R, Westerblad H, Larsson NG (2006) Respiratory chain dysfunction in skeletal muscle does not cause insulin resistance. *Biochem Biophys Res Commun* **350**, 202-207.

[215] Vernochet C, Mourier A, Bezy O, Macotela Y, Boucher J, Rardin MJ, An D, Lee KY, Ilkayeva OR, Zingaretti CM, Emanuelli B, Smyth G, Cinti S, Newgard CB, Gibson BW, Larsson NG, Kahn CR (2012) Adipose-specific deletion of TFAM increases mitochondrial oxidation and protects mice against obesity and insulin resistance. *Cell Metab* **16**, 765-776.

[216] Quintens R, Singh S, Lemaire K, De Bock K, Granvik M, Schraenen A, Vroegrijk IO, Costa V, Van Noten P, Lambrechts D, Lehnert S, Van Lommel L, Thorrez L, De Faudeur G, Romijn JA, Shelton JM, Scorrano L, Lijnen HR, Voshol PJ, Carmeliet P, Mammen PP, Schuit F (2013) Mice deficient in the respiratory chain gene Cox6a2 are protected against high-fat diet-induced obesity and insulin resistance. *PLoS One* **8**, e56719.

[217] Raule N, Sevini F, Li S, Barbieri A, Tallaro F, Lomartire L, Vianello D, Montesanto A, Moilanen JS, Bezrukov V, Blanche H, Hervonen A, Christensen K, Deiana L, Gonos ES, Kirkwood TB, Kristensen P, Leon A, Pelicci PG, Poulain M, Rea IM, Remacle J, Robine JM, Schreiber S, Sikora E, Eline Slagboom P, Spazzafumo L, Antonietta Stazi M, Toussaint O, Vaupel JW, Rose G, Majamaa K, Perola M, Johnson TE, Bolund L, Yang H, Passarino G, Franceschi C (2014) The co-occurrence of mtDNA mutations on different oxidative phosphorylation subunits, not detected by haplogroup analysis, affects human longevity and is population specific. *Aging Cell* **13**, 401-407.

[218] Copeland JM, Cho J, Lo T Jr, Hur JH, Bahadorani S, Arabyan T, Rabie J, Soh J, Walker DW (2009) Extension of Drosophila life span by RNAi of the mitochondrial respiratory chain. *Curr Biol* **19**, 1591-1598.

[219] Lee SS, Lee RY, Fraser AG, Kamath RS, Ahringer J, Ruvkun G (2003) A systematic RNAi screen identifies a critical role for mitochondria in C. elegans longevity. *Nat Genet* **33**, 40-48.

[220] Liu X, Jiang N, Hughes B, Bigras E, Shoubridge E, Hekimi S (2005) Evolutionary conservation of the clk-1-dependent mechanism of longevity: Loss of mclk1 increases cellular fitness and lifespan in mice. *Genes Dev* **19**, 2424-2434.

[221] Zhang L, Zhang S, Maezawa I, Trushin S, Minhas P, Pinto M, Jin LW, Prasain K, Nguyen TD, Yamazaki Y, Kanekiyo T, Bu G, Gateno B, Chang KO, Nath KA, Nemutlu E, Dzeja P, Pang YP, Hua DH, Trushina E (2015) Modulation of mitochondrial complex I activity averts cognitive decline in multiple animal models of familial Alzheimer's disease. *E Bio Medicine* **2**, 294-305.

[222] Baumgart M, Priebe S, Groth M, Hartmann N, Menzel U, Pandolfini L, Koch P, Felder M, Ristow M, Englert C, Guthke R, Platzer M, Cellerino A (2016) Longitudinal RNA-Seq analysis of vertebrate aging identifies mitochondrial complex i as a small-molecule-sensitive modifier of lifespan. *Cell Syst* **2**, 122-132.

[223] Mendiola-Precoma J, Berumen LC, Padilla K, Garcia-Alcocer G (2016) Therapies for prevention and treatment of Alzheimer's disease. *Biomed Res Int* **2016**, 2589276.

[224] Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H (2015) Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimers Dement* **11**, 718-726.

[225] Bertram S, Brixius K, Brinkmann C (2016) Exercise for the diabetic brain: How physical training may help prevent dementia and Alzheimer's disease in T2DM patients. *Endocrine* **53**, 350-363.

[226] Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, Cholerton BA, Plymate SR, Fishel MA, Watson GS, Duncan GE, Mehta PD, Craft S (2010) Aerobic exercise improves cognition for older adults with glucose intolerance, a risk factor for Alzheimer's disease. *J Alzheimers Dis* **22**, 569-579.

[227] Merry TL, Ristow M (2016) Mitohormesis in exercise training. *Free Radic Biol Med* **98**, 123-130.

[228] Ntsapi C, Loos B (2016) Caloric restriction and the precision-control of autophagy: A strategy for delaying neurodegenerative disease progression. *Exp Gerontol* **83**, 97-111.

[229] Van Cauwenberghe C, Vandendriessche C, Libert C, Vandenbroucke RE (2016) Caloric restriction: Beneficial effects on brain aging and Alzheimer's disease. *Mamm Genome* **27**, 300-319.

[230] Hanson AJ, Bayer JL, Baker LD, Cholerton B, VanFossen B, Trittschuh E, Rissman RA, Donohue MC, Moghadam SH, Plymate SR, Craft S (2015) Differential effects of meal challenges on cognition, metabolism, and biomarkers for apolipoprotein E ε4 carriers and adults with mild cognitive impairment. *J Alzheimers Dis* **48**, 205-218.

[231] Zhang L, Trushin S, Christensen TA, Bachmeier BV, Gateno B, Schroeder A, Yao J, Itoh K, Sesaki H, Poon WW, Gylys KH, Patterson ER, Parisi JE, Diaz Brinton R, Salisbury JL, Trushina E (2016) Altered brain energetics induces mitochondrial fission arrest in Alzheimer's Disease. *Sci Rep* **6**, 18725.

Scientific article analysis

titled: Oxidative Stress, Synaptic Dysfunction, and Alzheimer’s Disease

I-Molecular hallmarks of Alzheimer's disease:

- The cause of Alzheimer's disease is unknown, but there are factors that influence its occurrence, such as genetic factors, environmental pollutants, mitochondrial haplotypes, age and sex **(Kandimalla R.*et al*,2016) (Tramutola A; *et al*,2016)**

- The appearance of mutations in the genes that encode amyloid-β protein precursor (AβPP), or proteins presenilin 1 (PS1) and presenilin 2 (PS2) that form Aβ Peptides which are found in neurons, endoplasmic reticulum, mitochondrial membranes it is related to memory deficit. Thus, the effect on molecular mechanics leads to a dysfunction in the neuronal synapse in Alzheimer's disease. **(Selkoe DJ ,2008) (LaFerla FM; *et al*,2007)**

- Excessive phosphorylation of microtubule-stable Tau protein disrupts the neuronal trafficking machinery as transport of Tau protein to neuronal spines is associated with dysfunction causes Alzheimer's disease **(Andreadis A; *et al*,1992)**

- Alzheimer's disease can be diagnosed only by examining brain tissue after death for the presence of extracellular plaques formed by Aβ peptides, and intracellular neurofibrillary tangles (NFTs) consisting of hyperphosphorylated Tau protein with atrophy of brain regions. There is also a relationship between the presence of Tau protein with Aβ plaques and neurodegeneration. **(Selkoe DJ,2001)**

II-The role of oxidative stress in Alzheimer's disease

-According to the mitochondrial cascade hypothesis, in Alzheimer's disease, age-related mitochondrial function is affected, which affects the expression and processing of AβPP that accumulates Aβ. **(Swerdlow RH; *et al* 2014)**

- During Alzheimer's disease an abnormal mitochondrial axonal trafficking occurs with abnormalities in fission and fusion before the development of amyloid plaques or memory defects. **(Atamna H; Frey WH,2007)**

- With the use of tomography, glucose metabolism in the brain is reduced without any effect on the deposition of Aβ in the brain. **(Reiman EM; *et al*,2004)**

- Disruption of glucose metabolism during Alzheimer's disease associated with mitochondria may be a direct cause of oxidative stress or synaptic dysfunction without any evidence of Tau or Aβ defects. **(Reiman EM; *et al*,2004)– (Mosconi L; *et al*,2008)**

- Free energy is produced in the brain, specifically within the mitochondria, through the oxidation of glucose to enhance cellular interactions **(Jones DP, 2006)**

- Oxidative stress is a dysfunction of oxidants and antioxidants that is associated with increased production of both ROS and reactive nitrogen species (RNS) and other sources of oxygen production such as monoamine oxidase enzymes. **(Hauptmann. N et al,1996) (DiMeo. S *et al*,2016)**

- During the process of oxidative phosphorylation, O_2 and H_2O_2 are produced as byproducts in the mitochondria **(Quinlan CL *et al*,2013)** where antioxidant enzymes work to remove free radicals. Then the nuclear factor Nrf2 is activated, a nuclear factor that performs the process of cytoplasmic repression, where the protein KEAP1 is released, which is released to the nucleus, where it activates the transcription of genes that protect cells, which is what It increases the level of antioxidant enzymes and proteins such as glutathione-S-transferase **(Joshi G, Johnson JA,2012)**. However, despite the relationship of the factor Nrf2 to fighting oxidative stress, a decrease in its level has been recorded in Alzheimer's patients despite the presence of oxidative stress in some cases, as the mechanism is not precise enough to enable to be affected by the mechanisms of disease and aging **(Patel M ,2016) (Bhat AH ;*et al* ,2015).**

Figure 1 page 3:

The figure presents the mechanisms of reactive oxygen species production in the mitochondrial matrix and the role of antioxidants during oxidative phosphorylation.

The first and third complexes of the mitochondrial electron transport chain produce the superanion (O2–) during aerobic respiration.

Both (MnSOD) and (CuZnSOD) convert H_2O to H_2O_2 between the mitochondrial membrane and then H_2O_2 is reduced to water via glutathione peroxidase (GPX) detoxification.

Reductive glutathione (GSH) is used as the reductant by the GPX.

A reaction occurs between the resulting oxidized glutathione with another glutathione molecule to produce glutathione disulfide (GSSG) and then returns to its natural state as GSH through the enzyme glutathione reductase (GR).

- The activity of antioxidant enzymes changes in Alzheimer's patients, which leads to the accumulation of reactive oxygen species, causing oxidative stress **(Uttara B*; et al* ,2015).**

Indicators of oxidative stress such as oxidized proteins, accumulation of lipids and aldehydes, and oxidative stresses in RNA and mitochondrial DNA were found in brain tissue after death, which is evidence that mitochondrial damage contributes to Alzheimer's disease, so the accumulation of reactive oxygen species affects the whole cell **(Smith MA ;*et al*,1995) (Migliore L ; *et al*,2005).**

-The abnormal balance of biologically active minerals such as iron and copper contribute to the production of free radicals that cause oxidative stress and affect the ratio of both Aβ and Tau. **(Beal MF,2005).**

-Iron, copper and zinc levels are high in Alzheimer's patients due to neuronal imbalance, which increases tau and amyloid pathologies by affecting AβPP processing and increasing Aβ accumulation by binding to them **(Liu G,2006).**

-This increase in Aβ accumulation can also accelerate ROS production, leading to mitochondrial dysfunction **(Greenough MA; *et al*,2013)**

Figure 02 page 04: Molecular targets of ROS

The uncontrolled production of reactive oxygen within the mitochondria leads to a loss of synaptic activity and thus damage to the mitochondria by affecting the mitochondrial DNA, proteins and membranes.

Figure 03 page 05: Genetic and environmental risk factors and mitochondrial dysfunction

Environmental and genetic risk factors lead to Alzheimer's disease through the production of reactive oxygen species on mitochondrial function, protein oxidation, lipid peroxidation, inflammation and mtDNA damage, as well as abnormal production of Aβ and Tau proteins

III- Oxidative stress and Synaptic dysfunction in Alzheimer’s Disease:

-Synapses are areas specialized in transmitting nerve and chemical signals from one cell to another **(Szule JA; *et al*,2015).**

-During neurotransmission, neuromodulators such as acetylcholine and dopamine bind to postsynaptic cell receptors, where neurotransmission depends mainly on the strength and accuracy of cellular mechanisms through the removal of neurotransmitters and the synthesis of amino acids and Ca^{2+} H channels in the presynaptic membrane, and all these factors affect the efficiency of synaptic transmission **(Szule JA; *et al*,2015).**

-**Figure 04 page 6**: Structure of a synapse

Left: We have two neurons from brain tissue observed by electron microscopy, where the presynaptic cell contains a large number of synaptic vesicles with mitochondria in all the presynaptic and postsynaptic cells in the synapse.

Right: Glutamate represented in blue from presynaptic cells activates NMDA receptors in presynaptic and post-synaptic neurons that include AMPA (orange) and NMDA (green) receptors where glutamate is released by glial transporters (GLT-1) and then recycled into neurons and reassemble them within the synapse.

-Inadequate clearance of glutamate leads to excessive Ca2 entry and thus damage to synaptic mitochondria and ROS production, resulting in neuronal dysfunction.

-In Alzheimer's disease, memory is impaired due to inhibition of LTP and promotion of LTD within the hippocampus **(Jang SS. Chung HJ,2016)**

-Cognitive impairment in Alzheimer's patients is due to the loss of synapses in affected brain regions **(DeKosky ST, Scheff SW1990)**

-ROS, Aβ, and pTau affect the activity of the N-methyl-D-aspartate (NMDA) receptor **(Newcomer JW; *et al*,2000).**

-With aging, the function of NMDA receptors declines. In Alzheimer's, the neurotoxicity of Aβ reduces the amount of NMDA receptors with the flow of ca2+ **(Frankland PW, Bontempi B,2005)**

-Memantine, which does not inhibit acetylcholinesterase, has a low affinity for NMDA receptors **(Parsons MP, Raymond LA,2014)**

-Soluble types of Aβ bind to AMPA receptors and activate Ca2+, whereby altered uptake of these receptors leads to synaptic dysfunction (**Hsieh H; *et al* ,2006)**

-With the development of Alzheimer's disease, levels of the neurotransmitter GABA decrease and the enzymes that synthesize acetylcholine are inhibited (**Li Y; *et al* ,2016)**

-It has been confirmed that there is a direct link between Aβ and Tau neurotoxicity, oxidative stress and synaptic dysfunction in Alzheimer's development in plasma and brain tissue damage **(Trushina E, Mielke MM 2013)**

III-Therapeutic strategies for Alzheimer’s disease

-Current treatments for Alzheimer's disease depend on 3 types of cholinesterase inhibitors - donepezil, rivastigmine, and galantamine. **(Andreadis A; *et al*,1992)**

-All experiments to remove Aβ peptides were unsuccessful **(Cummings J; *et al*,2016)**

-Oxidative stress can be considered as an early symptom of Alzheimer's disease **(Padurariu M; *et al*,2013)**

-There is no anti-oxidant treatment for Alzheimer's **(SanchetiH; *et al*, 2014)**

-Vitamin C did not give promising results for this disease, but vitamin E showed positive results when compared to a placebo **(Arlt S, Muller; *et al*, 2014)**

-There is no definitive test to diagnose Alzheimer's disease in living individuals **(Tolonen M *et al*,1985).**

-Curcumin, a polyphenolic compound, has shown good results due to its antioxidant and anti-inflammatory properties.

-Oxidative balance with strict control of levels of reactive oxygen species production and protection and preservation of mitochondria from damage and dysfunction is essential to protect cells from oxidative stress and prevent Alzheimer's disease **(Mendiola-Precoma J; *et al* ,2016)**

-A healthy lifestyle, especially exercise, and dietary modification contribute to the maintenance of such molecular mechanisms as decreased oxidative stress, increased antioxidant capacity, increased anti-inflammatory effects and improved clearance of Aβ associated with Aβ regulated transporters. The authors also found that plasma Aβ levels are affected by the type of meal to reach Finally, to prevent the development of Alzheimer's disease **(Mendiola-Precoma J; *et al* ,2016)**

Conclusions

Finally, it must be emphasized that the study of the molecular mechanisms associated with different stages of the development of Alzheimer's disease confirms the existence of a significant effect of oxidative stress.

The role of ROS in basic neuroprotection should be monitored against the harmful effects of increased uncontrolled ROS production, which requires a greater understanding of these mechanisms and the development of study strategies to reduce nervous stress and degenerative diseases.

General conclusion

Our scientific research study, included a comprehensive and in-depth study of phytotherapy and their types of treatment, especially the two main types of treatment, such as aromatherapy through their essential oils or modern treatment using the active substance of plants that enter into the compositions of some drugs, our objective of this study was to determine the effectiveness of the treatment of medicinal plants against the nervous breakdown and its symptoms and the link between them, where we focused on anxiety and Alzheimer's Disease.

The outcome of our research was rich in many important points and conclusions, which we mention as follows:

- We discovered the long history of phytotherapy starting from traditional therapy to modern therapy and discovery of the active substances and knowledge of their therapeutic roles, which opened up prospects and openness to the possibility of relying on phytotherapy on widely, and to carry out many clinical trials and studies that have enabled us to make many drugs that contain the active compounds of medicinal plants.
- We have identified the pharmacological properties of active substances of medicinal plants, and their modes of action in organic are mostly by targeting neurotransmitters or enzymes.
- Essential oils used in aromatherapy can be considered as a complementary treatment that has many benefits, including that their side effects are not dangerous or even absent, as well as the possibility of using them in the treatment of symptoms of anxiety and depression such as lemon balm and bergamot essential oil.
- Essential oils have an important role in the treatment of symptoms of neurodegenerative diseases such as Alzheimer's and this is due to the fact that essential oils have many advantages, such as some of them are considered as antidepressants and inflammation and others have sedative effects.
- We identified the components of the nervous system and the limbic system responsible for perception and sensation and the interrelationship between it and the glands
- We determined the effect of oxidative stress on cells and its relationship to degenerative diseases such as Alzheimer's.
- We also made sure that the main cause of Alzheimer's disease is not known, but it is known that only affect the elderly, also there is no known or effective medicine to treat this disease that causes atrophy and death of brain neurons, but there are treatments

for its symptoms only, such as aromatherapy using essential oils, some of which have been shown to help relieve some symptoms.

After all this information that we have collected, we have been shown many milestones in the relationship of treatment with medicinal plants and the link between them, and from it to our own perspective, we believe that we should focus more on the treatment of medicinal plants and rely on essential oils and active substances in particular, in addition to the fact that we must do more comprehensive clinical trials and studies where we may able to expand the horizons of treatment with medicinal plants and may be able to find treatments or other benefits, such as finding an effective treatment for Alzheimer's disease.

Therefore, the phytotherapy have an essential role in the treatment of nervous breakdown, and in particular, in treating its symptoms, whether it is anxiety, depression, or even degenerative diseases such as Parkinson and Alzheimer's disease.

References

A

A. Krishna, R. Tiwari, S. Kumar Aromatherapy-an alternative health care through essential oils J Med Aromat Plant Sci, 22 (2000), pp. 798-804.

A.K. Singh (2006). Flower Crops: Cultivation and Management. New India Publishing. pp. 193–205. ISBN 978-81-89422-35-6.

A.N. Panche, et al, 2016 Panche, A N et al. “Flavonoids: an overview.” *Journal of nutritional* science vol. 5 e47. 29 Dec. 2016, doi:10.1017/jns.2016.41

Abayomi Sofowora, et al, 2013 the role and place of medicinal plants in the strategies for disease prevention A Sofowora E Ogunbodede A Onayade Sofowora et al., Afr J Tradit Complement Altern Med. (2013) 10(5):210-229 p

Abuhamdah, S., Huang, L., Elliott, M. S., Howes, M. J., Ballard, C., Holmes, C., Burns, A., Perry, E. K., Francis, P. T., Lees, G., and Chazot, P. L. Pharmacological profile of an essential oil derived from Melissa officinalis with anti-agitation properties: focus on ligand-gated channels. J Pharm Pharmacol. 2008;60(3):377-384.

Adams, R.P. (2007) Identification of Essential Oil Components by Gas Chromatography/Mass Spectrometry. 4th Edition Allured Publishing Corporation, Carol Stream.

Adibhatla RM et Hatcher JF, 2010 Adibhatla RM, Hatcher JF. Lipid oxidation and peroxidation in CNS health and disease: from molecular mechanisms to therapeutic opportunities. Antioxid Redox Signal. 2010;12: 125-169.

Aiken CT *et al* Aiken CT, Kaake RM, Wang X, et al. Oxidative stress-mediated regulation of proteasome complexes. Mol Cell Proteomics.

Alaa Hashim Younis Atee, 2020 portal.arid.my site

Alamy web site

Ali Thayer, 2020 chemistry1science, site Phenols 04 December 2020

Allen, N. J., & Barres, B. A. (2005). Signaling between glia and neurons: Focus on synaptic plasticity. Current Opinion in Neurobiology, 15, 542–548.

American Chemical Society web site

American Psychiatric Association

Anders Wessling, Joakim Ramsberg. The review of antidepressants Depression. 1st ed. Sweden: Dental and Pharmaceutical Benefits agenc; 2008. p. 1–112.

Anne Prigent, Médecine par les plantes : des traitements à manier avec prudence,2018.

A. Panche et al, 2016 Panche, A., Diwan, A., & Chandra, S. (2016). Flavonoids: An overview. Journal of Nutritional Science, 5, E47. doi:10.1017/jns.2016.41
Arnould-Taylor, W.E., 1981. "Aromatherapy for the Whole Person." UK: Stanley Thornes, pp: 22-26.

Atlas of medicinal and aromatic plants in Arabic world, 2012 a Book from the league of Arab states Arab center for studies of arid zones and dry lands ACSAD
Atwood CS et al., 1998 Atwood CS, Moir RD, Huang X, et al. Dramatic aggregation of Alzheimer abeta by Cu(II) is induced by conditions representing physiological acidosis. J Biol Chem. 1998;273:12817-12826.

Atwood CS et al., 2000 Atwood CS, Scarpa RC, Huang X, et al. Characterization of copper interactions with alzheimer amyloid beta peptides: identification of an attomolar-affinity copper binding site on amyloid beta1-42. J Neurochem. 2000;75:1219-1233.

Awad R, Levac D, Cybulska P, Merali Z, Trudeau VL, Arnason JT. Effects of traditionally used anxiolytic botanicals on enzymes of the gamma-aminobutyric acid (GABA) system. Can J Physiol Pharmacol. 2007;85:933–942.

B

B. A. Forbes, D. F. Sahm, A. S. Weissfeld. Bailey and Scott's Diagnostic Microbiology, 12th edn. Mosby Elsevier : St. Louis, 2007.

B. Pawlikowska-Pawlega, W. Ignacy Gruszecki, L. Misiak et al.,"Modification of membranes by quercetin, a naturally occurring flavonoid, via its incorporation in the polar head group,"Biochimica et Biophysica Acta—Biomembranes, vol. 1768, no. 9,pp. 2195–2204, 2007.

B. Wright, L. A. Moraes, C. F. Kemp et al., "A structural basis for the inhibition of collagen-stimulated platelet function by quercetin and structurally related flavonoids," British Journal of Pharmacology, vol. 159, no. 6, pp. 1312–1325, 2010.

B.A. Erwin et al. The internet: home to a severe population of individuals with social anxiety disorder? Anxiety Disorders (2004).

Babashahi M, Fayazi S, Aghel. N., Haghighizadeh MH. Effect of Aromatherapy on Anxiety Level Among Preoperative patients. Ahwaz Univ Med Sci J. 2010;9(68):507–16.

Bacher W. Scham als Name Palastinas. Jew Q Rev. 1906; 18:564–5.
Bagetta, G.; Morrone, L.A.; Rombolà, L.; Amantea, D.; Russo, R.; Berliocchi, L.; Sakurada, S.; Sakurada, T.; Rotiroti, D.; Corasaniti, M.T. Neuropharmacology of the essential oil of bergamot. Fitoterapia 2010, 81,453–461.

Bagli, E.; Goussia, A.; Moschos, M.M.; Agnantis, N.; Kitsos, G. Natural Compounds and Neuroprotection: Mechanisms of Action and Novel Delivery Systems. In Vivo 2016, 30, 535–547.

Baker GB, Coutts RT, McKenna KF, Sherry-McKenna RL. Insights into the mechanisms of action of the MAO inhibitors phenelzine and tranylcypromine: a review. J Psychiatry Neurosci. 1992 Nov;17(5):206-14.

Bakkali, F.; Averbeck, S.; Averbeck, D.; Idaomar, M. Biological effects of essential oils: A review. Food Chemistry Toxicology 2008, 46, 446–475.

Baris, O.; Güllüce, M.; Sahin, F.; Ozer, H.; Kılıc, H.; Ozkan, H.; Sökmen, M. and Ozbek, T. (2006). Biological activities of the essential oil and methanol extract of Achillea biebersteini Afan Afan (Asteraceae). Turkish J. Biol., Vol.30, pp.65-73.

Barker, P. J. (2003). Psychiatric and mental health nursing: The craft of caring. London: Arnold.

Barlow, D. H. (2002). (2nd ed.). Guilford Press.

Barnham KJ et Bush Al, 2008 Barnham KJ, Bush AI. Metals in Alzheimer's and Parkinson's diseases. Curr Opin Chem Biol. 2008;12:222-228.

Barton RA, (2014). Rapid evolution of the cerebellum in humans and other great apes.

Basch E, Foppa I, Liebowitz R, Nelson J, Smith M, Sollars D, et al: Lavender (Lavandula angustifolia Miller). J Herb Pharmacother 2004; 4:63–78.

Bedi, B. M. Jasmine flower-contact dermatitis. (Report of a case). Indian J.Dermatol. 1971; 16(3):61-62.

Bergquist H., Kallen B. (1954). Notes on the early histogenesis and morphogenesis of the central nervous system in vertebrates. J. Comp. Neurol. 100, 627–659

Berti, M., Wilckens, R., Pastene, E., Fischer, S., & Guerra, E. (2008). Yield and composition of Mentha x piperita L essential oil according to nitrogen fertilizer sources and rates in south-central Chile. Agro-Ciencia, 24, 58-71.

Bishop SJ, Duncan J, Lawrence AD. State anxiety modulation of the amygdala response to unattended threat-related stimuli. Journal of Neuroscience. 2004; 24(46):10364-10368.

Blanch, G. P., Flores, G., Caja, Mdel M., and Ruiz del Castillo, M. L. Jasminum polyanthum Franch. as a natural source of (-)-methyl jasmonate: an alternative to the use of the synthetic standard. Phytochem.Anal. 2009;20(5):427-433.

Bleakley S, Moghul S, Yeo S, Baldwin D. Suspected serotonin syndrome following treatment with fentanyl and venlafaxine. Progress in Neurology and Psychiatry 2011;15:36.

Bochkov VN et al., 2010 Bochkov VN, Oskolkova OV, Birukov KG, et al. Generation and biological activities of oxidized phospholipids. Antioxid Redox Signal. 2010;12:1009-1059.

Boehm K, Büssing A, Ostermann T. Aromatherapy as an adjuvant treatment in cancer care–a descriptive systematic review. Afr J Tradit Complement Altern Med. 2012; 9(4):503-18.

Botanica testing web site

Braak H, Braak E. Anatomy of the human hypothalamus (chiasmatic and tuberal region). Prog Brain Res. 1992;93:3-14; discussion 14-6.

Brookmeyer, E. Johnson, K. Ziegler-Graham, and H. M. Arrighi, “Forecasting the global burden of Alzheimer's disease,” Alzheimer's & Dementia, vol. 3, no. 3, pp. 186–191, 2007.

Burgunder, J.M. Neurodegeneration. IUBMB Life 2003, 55, 291.

Bystritsky A. Pharmacotherapy for generalized anxiety disorder in adults, 2018.

C

C. A. Rice-Evans, N. J. Miller, and G. Paganga, “Structure-antioxidant activity relationships of flavonoids and phenolic acids,” Free Radical Biology and Medicine, vol. 20, no. 7, pp. 933–956, 1996.

Carvalho LA, Gorenstein C, Moreno R, Pariante C, Markus RP., « Effect of antidepressants on melatonin metabolite in depressed patients. », J Psychopharmacol., no 23(3):315-21, mai 2009

Chrissie, W., 1996. “The Encyclopedia of Aromatherapy.” Vermont: Healing Arts Press, pp: 16-21

Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med. 1995 May 18;332(20):1351-62.

Chu Y et al., 2009 Chu Y, Dodiya H, Aebischer P, et al. Alterations in lysosomal and proteasomal markers in Parkinson's disease: relationship to alpha-synuclein inclusions. Neurobiol Dis. 2009;35:385-398.

Ciechanover A et Brundin P, 2003 Ciechanover A, Brundin P. The ubiquitin proteasome system in neurodegenerative diseases: sometimes the chicken, sometimes the egg. Neuron. 2003;40:427-446.

Cocco C, Brancia C, Corda G, Ferri GL. The Hypothalamic-Pituitary Axis and Autoantibody Related Disorders. Int J Mol Sci. 2017 Nov 03;18(11)

Corio, C. J. (1993). Enhance quality of life with aromatherapy [pamphlet]. (Availablefrom QLA, 800-688-8343)

Courtet, P., & Lopez-Castroman, J. (2017, October). Antidepressants and suicide risk in depression. World Psychiatry, 16(3).

Crino RD., Andrews G. Obsessive-compulsive disorder and axis I comorbidity. J Anxiety Disorders. 1996 ; 10(1) :37–46.

D

D. Jimbo, Y. Kimura, M. Taniguchi, M. Inoue, K. Urakami Effect of aromatherapy on patients with Alzheimer's disease Psychogeriatrics, 9 (2009), pp. 173-179

D. Tsoukalas, P. Fragkiadaki, A. O. Docea et al., “Association of nutraceutical supplements with longer telomere length,” International Journal of Molecular Medicine, vol. 44, no. 1, pp. 218–226, 2019.

D. Y. Chuang, M.-H. Chan, Y. Zong et al., “Magnolia polyphe nols attenuate oxidative and inflammatory responses in neurons and microglial cells,” Journal of Neuroinflammation, vol. 10, article 15, 2013.

Dae Young Yoo , Jung Hoon Choi, Woosuk Kim, Ki-Yeon Yoo, Choong Hyun Lee, Yeo Sung Yoon, Moo-Ho Won, In Koo Hwang. Department of Anatomy and Cell Biology, College of Veterinary Medicine, Seoul National University, Seoul, South Korea. Effects of Melissa officinalis L. (lemon balm) extract on neurogenesis associated with serum corticosterone and GABA in the mouse dentate gyrus.2011, 10.1007/s11064-010-0312-2.

Dahlmann B, 2007 Dahlmann B. Role of proteasomes in disease. BMC Biochem. 2007;8 Suppl 1:S3.

Dawidowicz, A.L., E. Rado, D. Wianowska, M. Mardarowicz and J. Gawdzik, 2008,Application of PLE for the determination of essential oil components from Thymus Vulgaris L. Talanta, 76: 878-884.

Deacon, Abramowitz, J. S, Cognitive and Behavioral Treatments for Anxiety Disorders: A Review of Meta-analytic Findings, Journal of Clinical Psychology, (2004). 60(4):429-41.

Deshpande, P.; Gogia, N.; Singh, A. Exploring the efficacy of natural products in alleviating Alzheimer’s disease. Neural Regen. Res. 2019, 14, 1321–1329.

Diana Wells, Anxiety: Breathing Problems and Exercises, 2020

Dick, A.J., H.H.N. Starmans, 1996. Extraction of secondary metabolites from plant material: a review. Trends Food Sci. Technol., pp: 191-197.

Dimitrova Z. The history of pharmacy. Sofija: St Clement of Ohrid; 1999. p. 13-26.

Dioscorides, Pedanius ; Goodyer, John (trad.) (1959). Gunther, R.T. (ed.). The Greek Herbal of Dioscorides. New York : Hafner Publishing. OCLC 3570794 doi:10.14662.

Donelian, A.; Carlson, L.H.C.; Lopes, T.J. & Machado, R.A.F. (2009). Comparison of extraction of patchouli (Pogostemon cablin) essential oil with supercritical CO2 and by steam distillation. The Journal of Supercritical Fluids, Vol.48, pp. 15-20.

Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol. 2001; 11:240–249

edition. Crossing Press, 2009.

E

Edzard E. The desktop guide to complementary and alternative medicine, 2ème edition, Grande-Bretagne, Ed. Mosby, 2001.
Ehrlich, Steven D. (January 2, 2015). "Lemon balm". University of Maryland Medical Center. Archived from the original on March 7, 2018. Retrieved June 23, 2017.

Erik Pigani, psychologies.com,2015.

Fahlbusch, Karl-Georg; Hammerschmidt, Franz-Josef; Panten, Johannes; Pickenhagen, Wilhelm; Schatkowski, Dietmar; Bauer, Kurt; Garbe, Dorothea; Surburg, Horst, 2003."Flavors and Fragrances". Ullmann's Encyclopedia of Industrial Chemistry.

F

Fakhry, H. A., Egyptian essential oils under revolution? In: IFEAT International Conference 2014. Rome, Italy September 204. London: IFEAT.

Falk, A.A., Hagberg, M.T., Löf, A.E., Wigaeus-Hjelm, E.M., Wang, Z.P., 1990. Uptake, distribution and elimination of alpha-pinene in man after exposure by inhalation. Scand J Work Environ Health 16, 372–378.

Fasipe, O. Neuropharmacological classification of antidepressant agents based on their mechanisms of action. Arc Med Heal Sci. 2018:6(1):81-94. DOI: 10.4103/amhs.amhs_7_18.

Faturi, C.B.; Leite, J.R.; Alves, P.B.; Canton, A.C.; Teixeira-Silva, F. Anxiolytic-like effect of sweet orange aroma in Wistar rats. Prog. Neuropsychopharmacol. Biol. Psychiatry 2010, 34, 605–609.

Faucon, M., Lobstein, A., 2015. Traité d'aromathérapie scientifique et médicale: fondements & aide à la prescription, 2e ed. Sang de la terre, Paris.

Ferreira-da-Silva, F.W.; da Silva-Alves, K.S.; Alves-Fernandes, T.A.; Coelho-de-Souza, A.N.; Leal-Cardoso, J.H. Effects of 1,8-cineole on Na(+) currents of dissociated superior cervical ganglia neurons. Neurosci. Lett. 2015, 595, 45–49.

Fisher, K. & Phillips, C. (2008). Potential antimicrobial uses of essential oils in food: is citrus the answer. Trends in Food Science & Technology, Vol.19, pp. 156-164.

Foa, E. B., & Powers, M. B. (2011). Center for the Treatment and Study of Anxiety. In J. C. Norcross, G. R. VandenBos, & D. K. Freedheim (Eds.), History of psychotherapy: Continuity and change (pp. 408–414).

Folk J, Folk M (ed.). "Anxiety symptoms – Fear of dying". Anxiety Centre. Archived from the original on March 5, 2009.

Forschende Komplementärmedizin / Research in Complementary Medicine, 17(3), 2-

Franchomme, P., 2015. La science des huiles essentielles médicinales. Guy Trédaniel, Paris.

FreemantleN., Mason J., Phillips T. et al. « Predictive value of pharmacological activity for the relative efficacy of antidepressants drugs. Meta-regression Analysis » Br J Psychiatry 2000; 177:292-302.

G

G. Chiva-Blanch, M. Urpi-Sarda, R. Llorach et al., "Differential effects of polyphenols and alcohol of red wine on the expression of adhesion molecules and inflammatory cytokines related to atherosclerosis: a randomized clinical trial," The American Journal of Clinical Nutrition, vol. 95, no. 2, pp. 326–334, 2012.

G. P. Kumar and F. Khanum, "Neuroprotective potential of phytochemicals," Pharmacognosy Reviews, vol. 6, no. 12, pp. 81–90, 2012.

Gabriel M, et al. Antidepressant discontinuation syndrome. Canadian Medical Association Journal. 2017; doi:10.1503/cmaj.160991.

Galli R, Gritti A, Bonfanti L, Vescovi AL. Neural stem cells: an overview. Circ Res. 2003 Apr 04;92(6):598-608.

Gantt WH. Measures of susceptibility to nervous breakdown. Am J Psychiatry. 2006 Apr;99(6):839-849.

Garcia-Jiménez N, Pérez-Alonso MJ, Velasco-Negueruela A. (2000) Chemical composition of fennel oil, Foeniculum vulgare,Miller from Spain. Journal of Essential Oil Research, 12, 159-162.

Gardiner SJ, Begg EJ. Pharmacogenetics, drug-metabolizingenzymes, and clinical practice. Pharmacol ,2006;58(3):521-90.

GBD. 2015 Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990-2015: A systematic analysis for the global burden of disease study 2015. Lancet Neurol. 2017, 16, 877–897.

gemmo-derivatives from plants and their biotherapeutical properties. ARJASR 2016, 85–92,

Generalić Mekinić, I.; Blažević, I.; Mudnić, I.; Burčul, F.; Grga, M.; Skroza, D.; Jerčić, I.; Ljubenkov, I.; Boban, M.; Miloš, M.; Katalinić, V., Sea fennel (Crithmum maritimum L.): phytochemical profile, antioxidative, cholinesterase inhibitory and vasodilatory activity. J. Food Sci. Technol.-Mysore, 2016.

Georges Sens-Olive, Les huiles principales - généralités et définitions in Traité de phytothérapie et d'aromathérapie, éd. Maloine, 1979, pp 141-142.

Ghaemi, S. N., Lenox, M. S., & Baldessarini, R. J. (2001). Effectiveness and safety of long-term antidepressant treatment in bipolar disorder. The Journal of Clinical Psychiatry, 62(7), 565–569.

Gnatta JR, Zotelli MFM, Carmo DRB, Lopes CLBC, Rogenski NM, Silva MJP. The use of aromatherapy to improve self-esteem. Rev Esc Enferm USP [Internet]. 2011 [cited 2015 July 21];45(5):1113-20.

Godin B, Touitou E. Transdermal skin delivery: predictions for humans from in vivo, ex vivo and animal models. Adv Drug Deliv Rev 2007; 59: 1152–1161.

Grant, Carlos Blanco, Deborah S. Hasin, Carlos Blanco, Frederick S. Stinson, Risë B Goldstein the Journal of Clinical Psychiatry, 2005. 66(11):1351-1361

Halliwell B: Free radicals, antioxidants and human disease: Curiosity, cause or consequence. Lancet 344:721-724, 1994

H

Harmer CJ, Duman RS, Cowen PJ. How do antidepressants work? New perspectives for refining future treatment approaches. Lancet Psychiatry. 2017 May;4(5):409-418.

Harvey, A. L., Clark, R. L., Mackay, S. P., & Johnston, B. F. (2010). Current strategies for drug discovery through natural products. Expert Opinion on Drug Discovery, 5(6), 559–568.

Harwood, Laurence, M., Moody, J. Christopher, 1989. Experimental organic chemistry: Principles and Practice (Illustrated ed.). Wiley-Blackwell., pp: 122-125. ISBN 0-632-02017-2.

Healy, D. The antidepressant tale: Figures signifying nothing? Adv Psychiatr Treat. 2006;12:320–328.

Healy, D., & Whitaker, C. (2003). Antidepressants and suicide: Risk-benefit conundrums. Journal of Psychiatry & Neuroscience, 28(5), 331–337.

Hébert, N., Gagné, F., C˘ ejka, P., Bouchard, B., Haussler, R., Cyr, D.G., Blaise, C., -Fournier, M., 2008. Effects of ozone, ultraviolet and peracetic acid disinfection of a primary-treated municipal effluent on the immune system of rainbow trout (Oncorhynchus mykiss). Comp. Biochem. Physiol. C Toxicol. Pharmacol. 148, 122–127.

Heemels, M.T. Neurodegenerative diseases. Nature 2016, 539, 179.

Herz Rachel S, Aromatherapy facts and fictions: a scientific analysis of olfactory effects on mood, physiology and behavior, Department of Psychiatry and Human Behavior, Warren Alpert Medical School, Brown University, Providence, Rhode Island (2009) .02912, USA.

Hesham H. A. Rassem , Abdurahman Nour, R. M. Yunus .Biological activities of essential oils ,2016.

Hirsch M, et al. Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects. 2019.

Hoehn-Saric, R., & McLeod, D. R. (1985). Locus of control in chronic anxiety disorders. Acta Psychiatrica Scandinavica, 72(6), 529–535

Hotz J, Enck P, Goebell H, Heymann-Monnikes I, Holtmann G, Layer P: [Consensus report: irritable bowel syndrome – definition, differential diagnosis, pathophysiology and therapeutic

possibilities. Consensus of the German society of digestive and metabolic diseases]. Z Gastroenterol 1999; 37: 685–700.

I

Ienco EC*et al.*, 2011 enco EC, LoGerfo A, Carlesi C, et al. Oxidative stress treatment for clinical trials in neurodegenerative diseases. J Alzheimers Dis. 2011;24 Suppl 2:111-126.

Ishola I., Chatterjee M., Tota S., Tadigopulla N., Adeyemi O.O., Palit G., Shukla R. Antidepressant and anxiolytic effects of amentoflavone isolated from Cnestis ferruginea in mice. Pharmacol. Biochem. Behav. 2012;103:322–331. doi: 10.1016/j.pbb.2012.08.017.

J

J. K. Kim, H. Bae, M.-J. Kim et al., "Inhibitory effect of pon- cirus trifoliate on acetylcholinesterase and attenuating activity against trimethyltin-induced learning and memory impairment," Bioscience, Biotechnology and Biochemistry, vol. 73, no.5, pp. 1105–1112, 2009.

Javorka, K., Tomori, Z., Zavarská, L., 1980. Protective and defensive airway reflexes in premature infants. Physiol Bohemoslov 29, 29–35.

Jean-Pierre Théallet (2016) Le guide familial des plantes qui soignent. Published by Albin Michel.

john R Keefe, Jun J Mao, Irene Soeller, and others (2016), "Short-term open-label chamomile (Matricaria chamomilla L.) Therapy of moderate to severe generalized anxiety disorder☆", Phytomedicine, Issue 14, Folder 23, Page 1699-1705.

Juga complementary therapies web site

Jung T et al., 2009 Jung T, Catalgol B, Grune T. The proteasomal system. Mol Aspects Med. 2009;30:191-296.

K

K. A. Jacobson, S. Moro, J. A. Manthey, P. L. West, and X.-D. Ji, "Interactions of flavones and other phytochemicals with adenosine receptors," Advances in Experimental Medicine and Biology, vol. 505, pp. 163–171, 2002.

K. Ono, Y. Yoshiike, A. Takashima, K. Hasegawa, H. Naiki, and M. Yamada, “Potent anti-amyloidogenic and fibril-destabilizing effects of polyphenols in vitro: implications for the prevention and therapeutics of Alzheimer’s disease,” Journal of Neurochemistry, vol. 87, no. 1, pp. 172–181, 2003.

Kanany M, Mazloom R, Emami A, Mokhber N. Lavender essential oils fragrance therapeutic effect on anxiety of patients undergoing hemodialysis[in persian]. J Nurs Midwife. 2011;10(3-4):63–71.

Kathi Keville and Mindy Green. Aromatherapy: A Complete Guide to the Healing Art, second

Kawasaki, H.; Mizuta, K.; Fujita, T.; Kumamoto, E. Inhibition by menthol and its related chemicals of compound action potentials in frog sciatic nerves. Life Sci. 2013, 92, 359–367.

Ke Y et Qian ZM, 2007 Ke Y, Qian ZM. Brain iron metabolism: neurobiology and neurochemistry. Prog Neurobiol. 2007; 83:149-173.

Keck S et al., 2003 Keck S, Nitsch R, Grune T, et al. Proteasome inhibition by paired helical filament-tau in brains of patients with Alzheimer's disease. J Neurochem. 2003 ;85:115-522.

Keller JN et al., 1997 Keller JN, Pang Z, Geddes JW, et al. Impairment of glucose and glutamate transport and induction of mitochondrial oxidative stress and dysfunction in synaptosomes by amyloid beta-peptide: role of the lipid peroxidation product 4-hydroxynonenal. J Neurochem. 1997; 69:273-284.

Kennedy, D.O.; Scholey, A.B. The Psychopharmacology of European herbs with cognition-enhancing properties. Curr. Pharm. Des. 2006, 12, 4613–4623.

Khan A, Warner HA, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials. Arch Gen Psychiatry. 2000;57:311–317. doi: 10.1001/archpsyc.57.4.311.

Klein, R. G., & Pine, D. S. (2001). Anxiety disorders. In M. Rutter, E. Taylor, & M. Hersov (Eds.), Child and adolescent psychiatry (3rd ed.). New York: Blackwell Scientific.

Kohlert, C., Schindler, G., März, R. W., Abel, G., Brinkhaus, B., Derendorf, H., … Veit, M. (2002). Systemic Availability and Pharmacokinetics of Thymol in Humans. The Journal of Clinical Pharmacology, 42(7), 731‑737.

Krishna A, Tiwari R, Kumar S. Aromatherapy-an alternative health care through essential oils. J Med Aromat Plant Sci 2000; 22: 798-804.

Kuo TC. A study about the inhibition effect of jasmine essential oil on the central nervous system. J Health Sci 2017;7:67-72.

L

L. Miao et D.K.S. Clair, 2009 L. Miao and D. K. S. Clair, "Regulation of superoxide dismutase genes: implications in disease," Free Radical Biology and Medicine, vol. 47, no. 4, pp. 344–356, 2009.

Lau, T.F., Leung, P.C., Wong, E.L. et al. Using herbal medicine as a means of prevention experience during.the SARS crisis. The American Journal of Chinese Medicine (2005b) 33 (3): p. 345–56 Starng C.

Lawless, J. (1997). The complete illustrated guide to aromatherapy. New York.

Lechan RM, Toni R. Functional Anatomy of the Hypothalamus and Pituitary. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. MDText.com, Inc.; South Dartmouth (MA): Nov 28, 2016.

Leonoudakis, D.; Rane, A.; Angeli, S.; Lithgow, G.J.; Andersen, J.K.; Chinta, S.J. Anti-Inflammatory and Neuroprotective Role of Natural Product Securinine in Activated Glial Cells: Implications for Parkinson's Disease. Mediat. Inflamm. 2017, 2017, 8302636.

Linda Mah, Claudia Szabuniewicz, Alexandra J Fiocco, Department of Geriatric Psychiatry, University of TorontobRotman Research Institute, Can anxiety damage the brain?,2016.

Lis-Balchin M, Hart S, Wan Hang Lo B. Jasmine absolute (Jasminum grandiflora L.) and its mode of

Lis-Balchin, M. 1997. "Essential Oils and 'Aromatherapy': Their Modern Role in Healing." Journal of the Royal Society for the Promotion of Health 177, no. 5: 324–29.

Lökk, J.; Nilsson, M. Frequency, type and factors associated with the use of complementary and alternative medicine in patients with Parkinson's disease at a neurological outpatient clinic. Parkinsonism Relat. Disord. 2010, 16, 540–544.

Lopez Castroman, Antidepressants and suicide risk in depression, World psychiatry: official journal of the World Psychiatric Association,2017.

Lotharius J et Brundin P, 2002 Lotharius J, Brundin P. Impaired dopamine storage resulting from alpha-synuclein mutations may contribute to the pathogenesis of Parkinson's disease. Hum Mol Genet. 2002; 11:2395-2407.

Lucia, A.; Guzmán, E. Emulsions containing essential oils, their components or volatile semiochemicals as promising tools for insect pest and pathogen management. Adv. Colloid Interface Sci. 2021, 287, 102330.

M

Maeda K, Ito T, Shioda S. Medical aromatherapy practice in Japan. Essence 2012 ; 10 : 14 6.

Mailhebiau, P., Soulier, J.-M., Azémar, J., 1992. Collège d'aromathérapie Philippe Mailhebiau : étude et prescription de la médecine aromatique. C. A. P. M. : Nouvelles presses internationales, Andouillé.

Menche N. (ed.) Biologie Anatomie Physiologie. Munich : Urban & Fischer/ Elsevier ; 2012.

Meyer-Warnod, B., 1984. Natural essential oils: extraction processes and application to some major oils. Perfume. Flavorist, 9: 93-104.

Milica Aćimović, dr Ljiljana Kostadinović, Naučni saradnik, Univerzitet u Novom Sadu,Naučni institut za prehrambene tehnologije, Bulevar cara Lazara 1, 21000 Novi Sad

Millet, Y., Jouglard, J., Steinmetz, M. D., Tognetti, P., Joanny, P., & Arditti, J. (1981). Toxicity of some essential plant oils. Clinical and experimental study. Clinical Toxicology, 18(12), 1485‑1498.

Miyazawa, M., Shindo, M., & Shimada, T. (2002). Metabolism of (+)- and (−)-Limonenes to respective Carveols and Perillyl Alcohols by CYP2C9 and CYP2C19 in Human Liver Microsomes. Drug Metabolism and Disposition, 30(5), 602‑607.

Miyazawa, M.; Watanabe, H.; Kameoka, H., Inhibition of Acetylcholinesterase Activity by Monoterpenoids with a p-Menthane Skeleton. J. Agric. Food Chem., 1997

Moja PL, Cusi C, Sterzi RR, Canepari C. Selective serotonin re-uptake inhibitors (SSRIs) for preventing migraine and tension-type headaches. Cochrane Database of Systematic Reviews 2005.

Moreno-Peral, Sonia Conejo, Maria Rubio-Valera, Ana Fernandez, Effectiveness of Psychological and/or Educational Interventions in the Prevention of Anxiety. A Systematic Review, Meta-analysis, and Meta-regression,(2017), JAMA Psychiatry 74(10).

Mwaniki, J. M. & Mbugua, S. N. (2007) Combined Solvent Extraction-Clevenger Distillation method.

N

Nathan Herrmann, Scott E Walker Current place of monoamine oxidase inhibitors in the treatment of depression,2013

National Association for Holistic Aromatherapy, Aromatherapy Journal, Herbal Infused Oils and Salves, 2013.

National Center for Complementary and Integrative Health: "Homeopathy''

Netdoctor web site

Nolte, J. (2002). The human brain: An introduction to its functional anatomy (5th ed.). St. Louis: Mosby.

Nowak D. Antioxidant plant polyphenols and cognitive disorders. In: Dietrich-Muszalska A., Chauhan V., Grignon S., editors. Studies on Psychiatric Disorders. New York, NY, USA: Humana Press; 2015.

O

Olicaworld website

Olpin .M,Stress Management for Life. 5th ed. Cengage Learning; 2020.

Oyemitan, I.A.; Elusiyan, C.A.; Akanmu, M.A.; Olugbade, T.A. Hypnotic, anticonvulsant and anxiolytic effects of 1-nitro-2-phenylethane isolated from the essential oil of Dennettia tripetala in mice. Phytomedicine 2013, 20, 1315–1322.

P

P. Pignatelli, A. Ghiselli, B. Buchetti et al., “Polyphenols synergistically inhibit oxidative stress in subjects given red and white wine,” Atherosclerosis, vol. 188, no. 1, pp. 77–83, 2006.

Panahi N, Mahmoudian M, Mortazavi P, Hashjin GS. Effects of berberine on beta-secretase activity in a rabbit model of Alzheimer's disease. Arch Med Sci [Internet] 2013;9(1):146–50.

Panda, S.S.; Jhanji, N. Natural Products as Potential anti-Alzheimer Agents. Curr. Med. Chem. 2018.

Perry N, Perry E. Aromatherapy in the management of psychiatric disorders clinical and neuropharmacological perspectives. CNS Drugs 2006; 20: 257-80.

Persani L. Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. J Clin Endocrinol Metab. 2012 Sep;97(9):3068-78.

pharmacomedicale web site

Pharmaonline web site

Phillips KA, Wilhelm S, Koran LM, Didie ER, Fallon BA, Feusner J, et al. Body dysmorphic disorder: Some key issues for DSM-V. Depression and Anxiety. 2010; 27:573–591.

phytothérapie, Larousse Médical, 2006.

Phytotherapy Research web site

Popa SL, Dumitrascu DL (2015) Anxiety and IBS revisited: ten years later. Clujul Med 88:253–257.

Poppek D et al., 2006 Poppek D, Keck S, Ermak G, et al. Phosphorylation inhibits turnover of the tau protein by the proteasome: influence of RCAN1 and oxidative stress. Biochem J. 2006; 400:511-520.

Pratico D, 2008 Pratico D. Oxidative stress hypothesis in Alzheimer's disease: a reappraisal. Trends Pharmacol Sci. 2008; 29:609-615.

Preskorn SH. Drug-drug interactions (DDIs) in psychiatric practice — Part 6: Pharmacodynamic considerations. Journal of Psychiatric Practice. 2019; doi:10.1097/PRA.0000000000000399.

Preskorn, S. H., & Irwin, H. A. (1982). Toxicity of tricyclic antidepressants—kinetics, mechanism, intervention: A review. The Journal of Clinical Psychiatry, 43(4), 151–156.

Querfurth HW et LaFerla FM, 2010 Querfurth HW, LaFerla FM. Alzheimer's disease. N Engl J Med. 2010;362:329-344.

R

R. Dringen et J. Hirrlinger, 2003 R. Dringen and J. Hirrlinger, “Glutathione pathways in the brain,” Biological Chemistry, vol. 384, no. 4, pp. 505–516, 2003.

R. Margis et al., 2008 R. Margis, C. Dunand, F. K. Teixeira, and M. MargisPinheiro, “Glutathione peroxidase family—an evolutionary overview,” FEBS Journal, vol. 275, no. 15, pp. 3959–3970, 2008.

Radulović, N.S.; Mladenović, M.Z.; Randjelovic, P.J.; Stojanović, N.M.; Dekić, M.S.; Blagojević, P.D., Toxic essential oils. Part IV: The essential oil of Achillea falcata L. as a source of biologically/pharmacologically active trans-sabinyl esters. Food Chem. Toxicol., 2015, 80, 114-129.

Rai, R. and B. Suresh, 2004. Indian Journal of Traditional Knowledge, 3(2): 187-191.

Raiciu, A.D.; Doina Vrabie, C.; Simona Negreş, S. Hystopathological and clinical investigations of five

Ramachandran, V. S. (Ed.). (2002). Encyclopedia of the human brain. San Diego, CA: Academic Press.

Rita Fjeldsted, Thomas William Teasdale, Martin Jensen, Suicide in Relation to the Experience of Stressful Life Events: A Population-Based Study, 2017-27849449.

Ritter J, Antidepressant drugs. In: Rang and Dale's Pharmacology. 9th ed. Elsevier; 2020.

Roth RS, Geisser ME, Bates R (2008) the relation of post-traumatic stress symptoms to depression and pain in patients with accident-related chronic pain. J Pain 9: 588–596.

Rynn, M. A., & Brawman-Mintzer, O. (2004). Generalized Anxiety Disorder: Acute and Chronic Treatment. CNS Spectrums, 9(10), 716–723.

S

S. Ramos, “Effects of dietary flavonoids on apoptotic pathways related to cancer chemoprevention,” Journal of Nutritional Biochemistry, vol. 18, no. 7, pp. 427–442, 2007.

S.-Z. Zhong, Q.-H. Ge, R. Qu, Q. Li, and S.-P. Ma, “Paeonol attenuates neurotoxicity and ameliorates cognitive impairment induced by d-galactose in ICR mice,” Journal of the Neurological Sciences, vol. 277, no. 1-2, pp. 58–64, 2009.

Saad B, Abu-Hijleh G, Suter UW. Cell culture techniques for assessing tissue compatibility of biomaterials. In: Arshady R (ed). Polymers in Medicine and Biotechnology, Volume 1. Polymer Chemistry and Biodegradation, Citus Books, 2003, 263–99.

Salvador GA et al., 2010 Salvador GA, Uranga RM, Giusto NM. Iron and mechanisms of neurotoxicity. Int J Alzheimers Dis. 2010;2011:720658.

Satish Valluri , Julie M Zito, Daniel J Safer, Ilene H Zuckerman, C Daniel Mullins, James J Korelitz , Food and Drug Administration pediatric suicidality warning on antidepressant and psychotherapy treatment for new-onset depression,2010

Schapira, A. H., & Olanow, C. W. (2004). Neuroprotection in Parkinson disease: Mysteries, myths, and misconceptions. JAMA, 291(3), 358–364.

Schiller C, Schiller D. 500 formulas for aromatherapy: mixing essential oils for every use. USA: Sterling Publications; 1994.

Schmahmann, J. D., & Pandya, D. N. (2006). Fiber pathways of the brain. New York: Oxford University Press.

Schmitt, S., Schäfer, U. F., Döbler, L., & Reichling, J. (2010). Variation of in vitro Human Skin Permeation of Rose Oil between Different Application Sites.

Schutter, D. J., & van Honk, J. (2005). The cerebellum on the rise in human emotion. Cerebellum, 4(4), 290–294.

Sedelnikova OA et al., 2010 Sedelnikova OA, Redon CE, Dickey JS, et al. Role of oxidatively induced DNA lesions in human pathogenesis. Mutat Res. 2010;704:152-159.

Semyanov A., Walker M.C., Kullmann D.M., Silver R.A. Tonically active GABA A receptors: Modulating gain and maintaining the tone. Trends Neurosci. 2004;27:262–269. doi: 10.1016/j.tins.2004.03.005.

Shan, C.S.; Zhang, H.F.; Xu, Q.Q.; Shi, Y.H.; Wang, Y.; Li, Y.; Lin, Y.; Zheng, G.Q. Herbal Medicine Formulas for Parkinson’s Disease: A Systematic Review and Meta-Analysis of

Randomized Double-Blind Placebo-Controlled Clinical Trials. Front. Aging Neurosci. 2018, 10, 349.

R

Simon, G.E. « Evidence review: efficacy and effectiveness of antidepressant treatment in primary care » General Hospital Psychiatry 2002; 24(4):213-24.

Singh B., Singh D., Goel R. K. Dual protective effect of *Passiflora incarnata* in epilepsy and associated post-ictal depression. *Journal of Ethnopharmacology.* 2012;139(1):273–279. doi: 10.1016/j.jep.2011.11.011.

Singh B., Singh D., Goel R. K. Dual protective effect of Passiflora incarnata in epilepsy and associated post-ictal depression. Journal of Ethnopharmacology. 2012;139(1):273–279. doi: 10.1016/j.jep.2011.11.011.

Singh, Ompal; Khanam, Zakia; Misra, Neelam; Srivastava, Manoj Kumar (2011). "Chamomile (Matricaria chamomilla L.): An overview". Pharmacognosy Reviews. 5 (9): 82–95 society, 4 (1): 12-26.

Soden K, Vincent K, Craske S, Lucas C, Ashley S. A randomized controlled trial of aromatherapy massage in a hospice setting. Palliat Med 2004;

Srivastava, P.; Yadav, R.S. Efficacy of Natural Compounds in Neurodegenerative Disorders. In Glutamate and ATP at the Interface of Metabolism and Signaling in the Brain; Springer Science and Business Media LLC: Berlin, Germany, 2016; Volume 12, pp. 107–123.

Stagkourakis S, Dunevall J, Taleat Z, Ewing AG, Broberger C. Dopamine Release Dynamics in the Tuberoinfundibular Dopamine System. J Neurosci. 2019 May 22;39(21):4009-4022

Starkov, A.A.; Beal, F.M. Portal to Alzheimer’s disease. Nat. Med. 2008, 14, 1020–1021.

Stein, D. J., Le Roux, L., Bouwer, C., & Van Heerden, B. (1998). Is olfactory reference syndrome an obsessive-compulsive spectrum disorder?: two cases and a discussion. J Neuropsychiatry Clin Neurosci, 10(1), 96-99.

Stein, M. B., & Sareen, J. (2015). Generalized anxiety disorder. The New England Journal of Medicine, 373(21), 2059–2068.

Stewart, D., & Vigod, S. (2017, August 11). Antenatal use of antidepressants and risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors (SSRIs).

Store.naturalelements web site

Susanne Fische, The hypothalamus in anxiety disorders Clinical Psychology and Psychotherapy, University of Zurich, Zurich, 2021

T

T. B. Joseph, S. W. J. Wang, X. Liu et al., "Disposition of flavonoids via enteric recycling: enzyme stability affects characterization of prunetin glucuronidation across species, organs, and UGT isoforms," Molecular Pharmaceutics, vol. 4, no. 6, pp. 883–894, 2007.View at: Publisher Site.

T. Dunning Aromatherapy: overview, safety and quality issues OA Altern Med, 1 (1) (2013), p. 6

T. I. Kim, Y. K. Lee, S. G. Park et al., "l-Theanine, an amino acid in green tea, attenuates β-amyloid-induced cognitive dysfunction and neurotoxicity: reduction in oxidative damage and inactivation of ERK/p38 kinase and NF-κB pathways," Free Radical Biology and Medicine, vol. 47, no. 11, pp. 1601–1610, 2009.

T. Sergent, N. Piront, J. Meurice, O. Toussaint, and Y.-J. Schneider, "Anti-inflammatory effects of dietary phenolic compounds in an in vitro model of inflamed human intestinal epithelium," Chemico-Biological Interactions, vol. 188, no. 3, pp. 659–667,2010.

Tamagno E et al., 2003 Tamagno E, Robino G, Obbili A, et al. H2O2 and 4-hydroxynonenal mediate amyloid beta-induced neuronal apoptosis by activating JNKs and p38MAPK. Exp Neurol. 2003; 180:144-155.

Tapsell LC. Health benefits of herbs and spices: the past, the present, the future. Med J Aust 2006 Aug.

Testa A, Giannuzzi R, Sollazzo F, Petrongolo L, Bernardini L, Daini S (February 2013). "Psychiatric emergencies (part I): psychiatric disorders causing organic symptoms". European Review for Medical and Pharmacological Sciences.

Thomas Sullivan, Editor of Policy and Medicine, President of Rock pointe Corporation Modern Medicine vs. Alternative Medicine: Different Levels of Evidence, May 6, 2018.

Thomas Sullivan, Institute of Medicine Report – The Future of Nursing: Leading Change, Advancing Health, INSTITUTE OF MEDICINE, 2018.

Tillfors M. Why do some individuals develop social phobia? A review with emphasis on the neurobiological influences. Nordic Journal of Psychiatry. 2004; 58:267–76.

Tobe EH, et al. Monoamine oxidase inhibitors: A clinical colloquy. Psychiatric Annals. 2014; doi:10.3928/00485713-20141208-07.

Torrico TJ, Munakomi S. Neuroanatomy, thalamus. StatPearls,2005

Tucakov J. Healing with plants. Beograd: Rad; 1990. p. 576-8.

Tucakov J. Pharmacognosy. Beograd: Institute for text book issuing in SR. Srbije; 1964. p. 11-30.

U

University of Idaho College of Science web site.

V

V. Conte et al., 2004 V. Conte, K. Uryu, S. Fujimoto et al., "Vitamin E reduces amyloidosis and improves cognitive function in Tg2576 mice following repetitive concussive brain injury," Journal of Neurochemistry, vol. 90, no. 3, pp. 758–764, 2004

Van Brederode, J.; Atak, S.; Kessler, A.; Pischetsrieder, M.; Villmann, C.; Alzheimer, C. The terpenoids Myrtenol and Verbenol act on subunit-containing GABAA receptors and enhance tonic inhibition in dentate gyrus granule cells. Neurosci. Lett. 2016, 628, 91–97.

Venkatesan, R.; Ji, E.; Kim, S.Y. Phytochemicals That Regulate Neurodegenerative Disease by Targeting Neurotrophins: A Comprehensive Review. Biomed Res. Int. 2015, 2015, 1–22.

Viljoen E, Visser J, Koen N, Musekiwa A. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. Nutr J. 2014 Mar 19;13:20. doi: 10.1186/1475-2891-13-20.

Vollebergh WA, Iedema J, Bijl RV, de Graaf R, Smit F, Ormel J. The structure and stability of common mental disorders: the NEMESIS study. Archives of General Psychiatry. 2001; 58(6):597–603.

Volz, H.-P., Müller, H., Sturm, Y., Preußler, B., & Möller, H.-J. (1995). Effect of initial treatment with antidepressants as a predictor of outcome after 8 weeks. Psychiatry Research, 58(2), 107–115.

W

W. Droge, 2002 Droge W. Free radicals in the physiological control of cell function. Physiological reviews. 2002; 82:47-95

W. Dröge, 2002 W. Droge, “Free radicals in the physiological control of cell ¨ function,” Physiological Reviews, vol. 82, no. 1, pp. 47–95, 2002.

Wakabayashi K et al., 2007 Wakabayashi K, Tanji K, Mori F, et al. The Lewy body in Parkinson's disease: molecules implicated in the formation and degradation of alpha-synuclein aggregates. Neuropathology. 2007; 27:494-506.

Wang Z.J., Levinson S.R., Sun L., Heinbockel T. Identification of both GABAA receptors and voltage-activated Na (+) channels as molecular targets of anticonvulsant α-asarone. Front. Pharmacol. 2014; 5:40. doi: 10.3389/fphar.2014.00040.

Werther, J., Saenger, M., Hartge, E. U., Ogada, T. & Siagi, Z. Combustion of agricultural residues. Prog. Energy Combust. Sci. 26, 1–27 (2000).

Wichtl M., Anton R. Plantes thérapeutiques – Tradition, pratique officinale, science et thérapeutique, 2ème édition, Ed. TEC & DOC, 2003.

Wildwood C. The encyclopedia of aromatherapy. Rochester: Healing Arts Press; 1996.

Wolk DA, et al. Clincal features and diagnosis of Alzheimer's disease https://www.uptodate.com/contents/search. Accessed Nov. 23, 2020.

World Health Organization

World Health Organization web site

Wynford-Thomas, R., & Robertson, N. P. (2017). The economic burden of chronic neurological disease. Journal of Neurology, 264(11), 2345–2347.

Y

Yuan H., Ma Q., Ye L., Piao G. The traditional medicine and modern medicine from natural products. Molecules. 2016; 21:559. doi: 10.3390/molecules21050559.

Yuki, Nobuhiro and Hans-Peter Hartung, "Guillain-Barré Syndrome," New England Journal of Medicine 366, no. 24 (2012): 2294-304.

Z

Zarifian, Mission générale concernant la prescription et l'utilisation des médicaments psychotropes en France. 1996. p. 274.

Zecca L et al., 2004 Zecca L, Youdim MB, Riederer P, et al. Iron, brain ageing and neurodegenerative disorders. Nat Rev Neurosci. 2004;5:863-873.

Zhang L.M., Wang H.L., Zhao N., Chen H.X., Li Y.F., Zhang Y.Z. Involvement of nitric oxide (NO) signaling pathway in the antidepressant action of the total flavonoids extracted fromXiaobuxin-Tang. Neurosci. Lett. 2014;575:31–36.

Zimmermann, T., Seiberling, M., Thomann, P., Karabelnik, D., 1995. [The relative bioavailability and pharmacokinetics of standardized myrtol]. Arzneimittelforschung 45, 1198–1201.

Ziosi P, Manfredini S, Vertuani S, Ruscetta V, Radice M, Sacchetti G. Evaluating essential oils in cosmetics: antioxidant capacity and functionality. Cosmet Toilet 2010.

Université Larbi Tébessi- Tébessa

Faculté des sciences exactes et des sciences de la nature et de la vie

Département de ...biologie appliquée

Filière : ..sciences biologiques

Année universitaire 2021/2022

Déclaration sur l'honneur de non-plagiat (A joindre obligatoirement avec le mémoire)

Je, soussigné(e)

Nom et prénom : Hamla Yahia

Régulièrement inscrit (e) : master 2

N de carte d'étudiant : 171734018900

Année universitaire : 2021/2022

Domaine : sciences de la nature et de la vie

Filière : sciences biologiques

Spécialité : toxicologie

Intitulé : How to use Herbal medicine to deal With a nervous break down

Atteste que mon mémoire est un travail original et que toutes les sources utilisées ont été indiquées dans leur totalité, je certifie également que je n'ai ni copié ni utilisé des idées ou des formulations tirées d'un ouvrage, article ou mémoire, en version imprimée ou électronique, sans mentionner précisément leur origine et que les citations intégrales sont signalées entre guillemets.

Sanctions en cas de plagiat prouvé :

L'étudiant sera convoqué devant le conseil de discipline, les sanctions prévues selon la gravité de plagiat sont :

- *L'annulation du mémoire avec possibilité de refaire sur un sujet différent.*
- *L'exclusion d'une année de Master.*
- *L'exclusion définitive.*

2022 جويلية 04

عن رئيس المجلس الشعبي البلدي
وبتفويض منه
إمضاء: معتوش
عون الإدارة الأقليمية

Fait à Tébessa, le :

Signature de l'étudiant (e)

Université Larbi Tébessi- Tébessa

Faculté des sciences exactes et des sciences de la nature et de la vie

Département de biologie appliquée

Filière : sciences biologiques

Année universitaire 2021/2022

Déclaration sur l'honneur de non-plagiat (A joindre obligatoirement avec le mémoire)

Je, soussigné(e)

Nom et prénom : Ilyes mohamed Rais

Régulièrement inscrit (e) : master 2

N de carte d'étudiant : 171734018610

Année universitaire : 2021/2022

Domaine : sciences de la nature et de la vie

Filière : sciences biologiques

Spécialité : toxicologie

Intitulé : How to use herbal medicine to deal with a nervous breakdown

Atteste que mon mémoire est un travail original et que toutes les sources utilisées ont été indiquées dans leur totalité, je certifie également que je n'ai ni copié ni utilisé des idées ou des formulations tirées d'un ouvrage, article ou mémoire, en version imprimée ou électronique, sans mentionner précisément leur origine et que les citations intégrales sont signalées entre guillemets.

Sanctions en cas de plagiat prouvé :

L'étudiant sera convoqué devant le conseil de discipline, les sanctions prévues selon la gravité de plagiat sont :

- *L'annulation du mémoire avec possibilité de refaire sur un sujet différent.*
- *L'exclusion d'une année de Master.*
- *L'exclusion définitive.*

2022 04

عن رئيس المجلس الشعبي البلدي
ينتشويش منه
إمضاء : معاوش رحمة
عون الإدارة الاقليمية

Fait à Tébessa, le :

Signature de l'étudiant (e)

Université Larbi Tébessi- Tébessa

Faculté des sciences exactes et des sciences de la nature et de la vie

Département de ..biologie.appliquée

Filière : ..sciences..biologiques

Année universitaire 2021/2022

Déclaration sur l'honneur de non-plagiat (A joindre obligatoirement avec le mémoire)

Je, soussigné(e)

Nom et prénom : Khelaifia AKram

Régulièrement inscrit (e) : Master 2

N de carte d'étudiant : 161633062738

Année universitaire : 2021/2022

Domaine : sciences de la nature et de la vie

Filière : sciences biologiques

Spécialité : toxicologie

Intitulé : How to use Herbal medecine to deal with a nervous breakdown

Atteste que mon mémoire est un travail original et que toutes les sources utilisées ont été indiquées dans leur totalité, je certifie également que je n'ai ni copié ni utilisé des idées ou des formulations tirées d'un ouvrage, article ou mémoire, en version imprimée ou électronique, sans mentionner précisément leur origine et que les citations intégrales sont signalées entre guillemets.

Sanctions en cas de plagiat prouvé :

L'étudiant sera convoqué devant le conseil de discipline, les sanctions prévues selon la gravité de plagiat sont :

- *L'annulation du mémoire avec possibilité de refaire sur un sujet différent.*
- *L'exclusion d'une année de Master.*
- *L'exclusion définitive.*

2022 جويلية 04

عن رئيس المجلس الشعبي البلدي
وبتفويض منه
الملحقة : بشوش رحيمة
عون الإدارة الاقليمية

Fait à Tébessa, le :

Signature de l'étudiant (e)

الجمهورية الجزائرية الديمقراطية الشعبية
République Algérienne Démocratique et Populaire
وزارة التعليم العالي و البحث العلمي
Ministère de l 'Enseignement Supérieur et de la Recherche Scientifique

UNIVERSITÉ LARBI TEBESSI - TÉBESSA

جامعة العربي التبسي-تبسة

المكتبة الجامعية المركزية

معلومات حول الأطروحة أو المذكرة

الاسم: يحي، الياس، أكرم

اللقب: حملة، رايس، خلايفية

الكلية: كلية العلوم الدقيقة وعلوم الطبيعة والحياة

القسم: البيولوجيا التطبيقية

التخصص: علم السموم

المستوى: ماستر 2

رقم الهاتف: 0668261806, 0655436974,0667829501

عنوان الإيمايل: yh19992020@gmail.com
mouhamedrais1999@gmail.com

khelaifiaakram27@gmail.com

عنوان المذكرة أو الأطروحة:

How to use herbal medicine to deal with nervous breakdown

المؤطر:Rouabhi Rachid-Sarra Zouaoui

الكلمات المفتاحية: phytotherapy, nervous breakdown, aromatherapy, essential oils, medicinal plants, nervous system, antidepressants, anxiety, Alzheimer.

تاريخ المناقشة للأطروحة: 2021/06/15

السنة الجامعية: 2021/2022

ملخص:

منذ العصور القديمة، كان العلاج بالنباتات من أكثر العلاجات شيوعًا وفائدة للإنسان حيث تطورت طرق العلاج بالنباتات

الطبية من الحضارات القديمة حتى العصر الحديث بالتوازي مع تطور التقنيات للاستفادة من المكونات الأساسية للنباتات

الطبية، وخاصة القلويدات، الفلافونويد والفينولات، وصولا إلى ظهور العلاج بالروائح من خلال الزيوت الأساسية للنباتات الطبية.

أجرينا هذه الدراسة لتقييم قدرة وتأثير العالج بالنباتات على الانهيار العصبي وأعراضه إضافة الى الامراض التنكسية، لتحديد الارتباط بينها.

لدراسة دور الأعشاب الطبية في مواجهة الانهيارات العصبية والأمراض المصاحبة لها، قمنا بإجراء العديد من الأبحاث، بدءاً بعموميات حول طب الأعشاب وأنواعها والمواد الفعالة للنباتات الطبية، بالإضافة إلى العالج بالروائح وطرق استخلاص الزيوت العطرية وأهميتها في الحد من الأمراض العصبية وآثارها.

في الفصل الثاني تدور دراستنا حول بنية الجهاز العصبي المركزي، وتأثير الانهيار العصبي عليه، وتحديد فاعلية الأعشاب الطبية في الحد من هذا المرض وآثاره، بالإضافة إلى آلية عمل مضادات الاكتئاب وآثارها السلبية وتقديم مفهوم حول الاجهاد التأكسدي واسبابه.

عرضنا في الفصل الأخير مرضين عصبيين مصاحبين للانهيار العصبي وهما القلق والزهايمر وآلية تأثير بعض النباتات الطبية مثل البابونج والخزامى في الوقاية والعلاج من هذه الأمراض.

في النهاية تم تحديد العلاقة بين استخدام الأدوية العشبية والانهيار العصبي، حيث يمكن علاج أعراض الانهيار العصبي بالنباتات الطبية وقد ثبت ذلك من خلال العديد من التجارب العلمية، ومن بين الأمراض التي يمكن أن تساعد النباتات الطبية في علاجها: الاكتئاب والقلق والعصبية والامراض التنكسية وهذا يعود لخصائص العديد من النباتات الطبية، بما في ذلك المهدئات والمنشطات والمثبطات وغيرها التي تستهدف النواقل العصبية.

كلمات مفتاحية: العلاج بالنباتات، الانهيار العصبي، العلاج بالروائح، الزيوت الأساسية، النباتات الطبية، الجهاز العصبي، مضادات الاكتئاب، القلق، الزهايمر، الأمراض التنكسية.

Résumé*:*

Depuis l'Antiquité, la phytothérapie est l'un des traitements les plus courants et les plus bénéfiques pour l'homme où les méthodes de traitement des plantes médicinales se sont développées depuis les civilisations anciennes jusqu'à l'ère moderne en parallèle avec le développement des techniques pour profiter des composants de base des plantes médicinales, notamment les alcaloïdes, les flavonoïdes et les phénols, jusqu'à l'émergence de l'aromathérapie à travers les huiles essentielles de plantes médicinales**.**

Nous avons mené cette étude pour évaluer la capacité et l'effet de la phytothérapie sur la dépression nerveuse et ses symptômes, afin de déterminer le lien entre eux**.**

Pour étudier le rôle des herbes médicinales contre les dépressions nerveuses et les maladies qui y sont associées, nous avons mené diverses recherches, en commençant par des généralités sur la phytothérapie, ses types et les substances actives des plantes médicinales, en plus de l'aromathérapie, des méthodes d'extraction des huiles essentielles et leur importance dans la réduction des maladies nerveuses et leurs effets**.**

Dans le second chapitre, notre étude tourne autour la structure du système nerveux central, de l'effet de la dépression nerveuse sur celui-ci, et de la détermination de l'efficacité des herbes médicinales pour réduire cette maladie et ses effets, en plus du mécanisme d'action des antidépresseurs et leurs effets négatifs**.**

Dans le dernier chapitre, nous avons présenté deux maladies neurologiques associées à la dépression nerveuse, à savoir l'anxiété et la maladie d'Alzheimer, et le mécanisme de l'effet de certaines plantes médicinales comme la camomille et la lavande dans la prévention et le traitement de ces maladies**.**

En fin de compte, la relation entre l'utilisation de la phytothérapie et la dépression nerveuse a été déterminée, où les symptômes de la dépression nerveuse peuvent être traités avec des plantes médicinales et cela a été prouvé par de nombreuses expériences scientifiques, et parmi les symptômes que les plantes médicinales peuvent aider à traiter sont la dépression, l'anxiété et la nervosité et cela est dû aux propriétés de nombreuses plantes médicinales, notamment les sédatifs, les stimulants, les dépresseurs, et autres**...**

Mots clés : phytothérapie, dépression nerveuse, aromathérapie, huiles essentielles, plantes médicinales, système nerveux, antidépresseurs, anxiété, Alzheimer**.**

Abstract*:*

Since ancient times, phytotherapy has been one of the most common and beneficial treatments for humans as the methods of treating medicinal plants developed from ancient civilizations until modern times in parallel with the development of techniques to benefit from the basic components of medicinal plants, especially alkaloids, flavonoids and phenols, leading to the emergence of aromatherapy through the essential oils of medicinal plants*.*

We conducted this study to evaluate the ability and effect of phytotherapy on nervous breakdown and its symptoms, to determine the link between them*.*

To study the role of medicinal herbs against nervous breakdowns and the diseases associated with it, we conducted various researches, starting with generalities about phytotherapy, its types and the active substances of medicinal plants, in addition to aromatherapy, methods of extracting essential oils and their importance in reducing nervous diseases and their effects*.*

In the second chapter, our study revolves around the structure of the central nervous system, the effect of nervous breakdown on it, and determining the effectiveness of medicinal herbs in reducing this disease and its effects, in addition to the mechanism of action of antidepressants and their negative effects*.*

In the last chapter, we presented two neurological diseases associated with nervous breakdown, namely anxiety and Alzheimer's, and the mechanism of the effect of some medicinal plants such as chamomile and lavender in the prevention and treatment of these diseases*.*

In the end, the relationship between the use of phytotherapy and nervous breakdown was determined, where the symptoms of nervous breakdown can be treated with medicinal plants and this has been proven through many scientific experiments, and among the symptoms that medicinal plants can help in treating are depression, anxiety and nervousness and this is due to the properties of Many medicinal plants, including sedatives, stimulants, depressants, and others*...*

Key words: phytotherapy, nervous breakdown, aromatherapy, essential oils, medicinal plants, nervous system, antidepressants, anxiety, Alzheimer*.*

Université Larbi Tébessi- Tébessa

Faculté des sciences exactes et des sciences de la nature et de la vie

Département de ...biologie appliquée

Filière : ..sciences biologiques

Année universitaire 2021/2022

Déclaration sur l'honneur de non-plagiat (A joindre obligatoirement avec le mémoire)

Je, soussigné(e)

Nom et prénom : Hamla Yahia

Régulièrement inscrit (e) : master 2

N de carte d'étudiant : 171734018900

Année universitaire : 2021/2022

Domaine : sciences de la nature et de la vie

Filière : sciences biologiques

Spécialité : toxicologie

Intitulé : How to use Herbal medicine to deal With a nervous break down

Atteste que mon mémoire est un travail original et que toutes les sources utilisées ont été indiquées dans leur totalité, je certifie également que je n'ai ni copié ni utilisé des idées ou des formulations tirées d'un ouvrage, article ou mémoire, en version imprimée ou électronique, sans mentionner précisément leur origine et que les citations intégrales sont signalées entre guillemets.

Sanctions en cas de plagiat prouvé :

L'étudiant sera convoqué devant le conseil de discipline, les sanctions prévues selon la gravité de plagiat sont :

- *L'annulation du mémoire avec possibilité de refaire sur un sujet différent.*
- *L'exclusion d'une année de Master.*
- *L'exclusion définitive.*

2022 جويلية 04

عن رئيس المجلس الشعبي البلدي
وبتفويض منه
إمضاء: معتوش
عون الإدارة الأقليمية

Fait à Tébessa, le :

Signature de l'étudiant (e)

Université Larbi Tébessi- Tébessa

Faculté des sciences exactes et des sciences de la nature et de la vie

Département de biologie appliquée

Filière : sciences biologiques

Année universitaire 2021/2022

Déclaration sur l'honneur de non-plagiat (A joindre obligatoirement avec le mémoire)

Je, soussigné(e)

Nom et prénom : Ilyes mohamed Rais

Régulièrement inscrit (e) : master 2

N de carte d'étudiant : 171734018610

Année universitaire : 2021/2022

Domaine : sciences de la nature et de la vie

Filière : sciences biologiques

Spécialité : toxicologie

Intitulé : How to use herbal medicine to deal with a nervous breakdown

Atteste que mon mémoire est un travail original et que toutes les sources utilisées ont été indiquées dans leur totalité, je certifie également que je n'ai ni copié ni utilisé des idées ou des formulations tirées d'un ouvrage, article ou mémoire, en version imprimée ou électronique, sans mentionner précisément leur origine et que les citations intégrales sont signalées entre guillemets.

Sanctions en cas de plagiat prouvé :

L'étudiant sera convoqué devant le conseil de discipline, les sanctions prévues selon la gravité de plagiat sont :

- *L'annulation du mémoire avec possibilité de refaire sur un sujet différent.*
- *L'exclusion d'une année de Master.*
- *L'exclusion définitive.*

2022 04

عن رئيس المجلس الشعبي البلدي
ينتشويش منه
إمضاء : معاوش رحمة
عون الإدارة الاقليمية

Fait à Tébessa, le :

Signature de l'étudiant (e)

Université Larbi Tébessi- Tébessa

Faculté des sciences exactes et des sciences de la nature et de la vie

Département de ..biologie.appliquée

Filière : ..sciences..biologiques

Année universitaire 2021/2022

Déclaration sur l'honneur de non-plagiat (A joindre obligatoirement avec le mémoire)

Je, soussigné(e)

Nom et prénom : Khelaifia AKram

Régulièrement inscrit (e) : Master 2

N de carte d'étudiant : 161633062738

Année universitaire : 2021/2022

Domaine : sciences de la nature et de la vie

Filière : sciences biologiques

Spécialité : toxicologie

Intitulé : How to use Herbal medecine to deal with a nervous breakdown

Atteste que mon mémoire est un travail original et que toutes les sources utilisées ont été indiquées dans leur totalité, je certifie également que je n'ai ni copié ni utilisé des idées ou des formulations tirées d'un ouvrage, article ou mémoire, en version imprimée ou électronique, sans mentionner précisément leur origine et que les citations intégrales sont signalées entre guillemets.

Sanctions en cas de plagiat prouvé :

L'étudiant sera convoqué devant le conseil de discipline, les sanctions prévues selon la gravité de plagiat sont :

- *L'annulation du mémoire avec possibilité de refaire sur un sujet différent.*
- *L'exclusion d'une année de Master.*
- *L'exclusion définitive.*

2022 جويلية 04

عن رئيس المجلس الشعبي البلدي
وبتفويض منه
الملحقة : بشوش رحيمة
عون الإدارة الاقليمية

Fait à Tébessa, le :

Signature de l'étudiant (e)