*Invited Review*

# ESSENTIAL OILS AS MODIFIERS OF HUMAN BEHAVIOR[1]

# [ACEITES ESENCIALES COMO MODIFICADORES DEL COMPORTAMIENTO HUMANO]

**María Andrea Castillo[1,2], Yenddy Carrero[3], Kendy Eduardo Urdaneta[1,2,4], Mathieu Renouf[3,5], Charly Lubin[3,5], Montiel Nola[2] and Neomar Semprún-Hernández[1,2,3,*]**

*[1] Research Division, Autism Immunology Unit of Maracaibo, 4001, Maracaibo, Venezuela. Email: neomar.semprun@gmail.com*
*[2]Cátedra Libre de Autismo, Vicerrectorado Académico, Universidad del Zulia, 4001, Maracaibo, Venezuela*
*[3]Laboratorio de Biología Molecular y Celular. Facultad de Ciencias de la Salud. Universidad Técnica de Ambato. Ambato-Ecuador*
*[4]Departamento de Biología, Facultad Experimental de Ciencias, Universidad del Zulia, Maracaibo, Venezuela*
*[5]Faculté de Médecine et de Pharmacie. Université de Poitiers. Poitiers-France*
**Corresponding author*

## SUMMARY

The aim of this review was to know the effect, properties and mechanism of action of essential oils in order to enhance their use as a treatment and adjuvant in some neurodegenerative pathologies and others associated to stress and human behavior, based on clinical trials and descriptive research. Some studies suggest that essential oils have been widely used in various applications, mainly in the pharmaceutical, cosmetic, food and agricultural industries since middle age. At the same time, based on human and animal studies has been established the effects of some essential oils about their behavior in the treatment of depression, anxiety, schizophrenic, sleep disorders in the regulation of mood modulating several neurotransmitters such as serotonin, noradrenaline, dopamine, glutamate, and gamma-aminobutyric acid also in some degenerative diseases such as Parkinson's or Alzheimer, as well as in the associated behaviors in depressive disorders, Autism spectrum disorder, ADHD, drugs addictions, people with stress and sleep disorders.

**Keywords:** essential oils, behavior, depression, anxiety, autism, ADHD, Parkinson's, Alzheimer

## RESUMEN

Esta revisión tiene como objetivo conocer el efecto, propiedades y mecanismo de acción de los aceites esenciales para potenciar su uso como tratamiento y coadyuvante en algunas patologías neurodegenerativas y otras asociadas al estrés y al comportamiento humano, basado en ensayos clínicos y trabajos descriptivos. Algunos estudios sugieren que desde la edad media, los aceites esenciales han sido ampliamente utilizados en diversas aplicaciones, principalmente en las industrias farmacéutica, cosmética, alimentaria y agrícola. Al mismo tiempo, a partir de estudios en humanos y animales se han establecido los efectos de algunos aceites esenciales sobre el comportamiento en el tratamiento de la depresión, ansiedad, esquizofrenia, trastornos del sueño y en en la regulación del estado de ánimo modulando varios neurotransmisores: serotonina, noradrenalina, dopamina, glutamato y ácido gamma-aminobutírico; también en algunas enfermedades degenerativas como el Parkinson o el Alzheimer, así como en los comportamientos asociados en los trastornos depresivos, trastornos del espectro autista, trastorno de déficit de atención con hiperactividad (TDAH) , adicciones a las drogas, personas con estrés y trastornos del sueño.

**Palabras clave:** aceites esenciales, comportamiento, depresión, ansiedad, autismo, TDAH, Parkinson, Alzheimer

[1] *Submitted May 22, 2017 – Accepted August 20, 2017.* 

## INTRODUCTION

New active substances research are rapidly increasing, this leads us to study medicinal plants and to improve in the production of the herbal plants constituents with beneficial biological activity, World Health Organization reported that, medicinal plants are the best source of drugs (WHO, 2010). Nevertheless, these molecules must be highly investigated about its pharmacokinetics, mechanism of action, tolerability, clinical drug–drug Interactions, effects, adverse effects, contraindications, salient features and safety. Pain is one of the main problems of various diseases (Chevalier, 1996), the pain can be physical or neurological and psychiatric, being produce by depression, anxiety, stress, schizophrenia, Alzheimer, insomnia and convulsions (Kourosh et al., 2014) and how these essential oils might be used in the treatment of abnormal behavior understanding how to modulate it's pathophysiology. The aim of this review was to describe the effect of some essential oils on human behavior

## ST. JOHN'S WORT ESSENTIAL OIL (*Hypericum perforatum* L.)

**Taxonomy:** Family: *Hypericaceae* - Genus: *Hypericum* - Specie: *H. perforatum*.

**Active compounds behavior modifiers:** hyperforin, hypericin, and pseudohypericin.

**Effects on human behavior and animal models:** regulation of mood, motivation, and reward, drugs addictions, anxiolytic, sedative, nootropic activities, anti-depressive, anti-schizophrenic and anti-nociceptive effects

*Hypericum perforatum L.*, also known as hypericum or St. John's Wort, is a herbaceous perennial plant native to Europe and Asia, recently introduce in North America (Barnes et al., 2001), nowadays it has a worldwide distribution (Patocka, 2003). There are many pharmacologicals active compounds that could be extracted from the roots, leaves and flowers such as flavonoids derivated as flavonols, flavones and glycosides biflavonoids including biapigeninand amentoflavone (Berghöfer and Hölzl, 1987). Tannins like Proanthocyanidins, the condensed type, have been reported (Bisset, 1994). Other phenols and volatile oils for example methyl-2-octane, *n*-nonane and traces of methyl-2-decane. Acids (isovalerianic, nicotinic, myristic, palmitic, stearic), carotenoids, choline, nicotinamide, pectin, b-sitosterol, straight chain saturated hydrocarbons and alcohols (Brondz et al., 1983).

However the major active pharmacological compounds of the extract are considered into two groups. The first one arehypericin, pseudohypericin and isohypericin (a naphthodianthrone), respectively present in fresh material (Vanhaelen and Vanhaelen-Fastre, 1983). Hypericin is considered to be the most important active ingredient. However, hypericin has only been shown to have activity (e.g.monoamine oxidase inhibitor) *in vitro* and has failed to exert detectable effects in animal models (Butterweck and Schmidt, 2007). The second one active constituents are hyperforin (a prenylatedphloroglucinol), adhyperforin (Ayuga and Rebuelta 1986; American Herbal Pharmacopeia, 1997) and oxygenated analogues of hyperforin (Verotta et al., 2000). Experimentally, hyperforin, inhibit reuptake of several neurotransmitters such as serotonin, noradrenaline, dopamine, glutamate, and gamma-aminobutyric acid *in vitro* and *in vivo* many of which are involved in the regulation of mood, motivation, and reward (Capasso et al., 2003).

Preclinical studies on the central nervous system activity of *Hypericum perforatum L.* (Hp) extracts suggest that it also displays anxiolytic, sedative, nootropic, antischizophrenic, anticonvulsant, antidiabetic, and analgesic activities and that it may be beneficial in the treatment of alcohol, nicotine, and caffeine addiction in experimental animals (Can et al., 2011; Can and Ozkay, 2012) moreover has anti-inflammatory, wound healing and anti-nociceptive effects (Motallebnejad et al., 2008; Suntar et al., 2010). Also is describe to prevent Alzheimer's disease, hypericin may interfere with the processes of polymerization of beta-amyloid peptide responsible for the onset of Alzheimer's disease (Griffith et al., 2010). Recent clinical studies found Hp extracts to be efficacious and well tolerated in the treatment of mild to moderate depressive episodes and for the short-term treatment of symptoms in mild depressive disorders (Luo, 2004; Kasper et al.,2010; Chen et al., 2011). The pharmacokinetics of hyperforin, hypericin, and pseudohypericin, the components of Hp extracts that are presumed to be responsible for its pharmacological effects, has been studied and despite structural similarity, hypericin, pseudohypericin, and hyperforin exhibit pharmacokinetic differences. After oral administration of singledoses of a range from 300-1800mg of Hp extract (0.3% of hypericin), hypericin was detectable in the blood after1.3h, and peak plasma concentrations were reachedafter ~4.6 h and steady-state levels by 4 days (Staffeldt et al., 1994; Brochmoller et al., 1997; Upton, 1997). The plasmahalf-life of hypericin is reported to be ~25h (Nangia et al., 2000). Although the bioavailability of hypericin is~14%, the therapeutic concentration of hypericin in brain remains unknown, and although it has been suggested that brain levels reach only 5% of plasma levels, hypericin'shalf-life in the brain may be weeks (Upton, 1997).

Hyperforin is reported to have antibacterial activity against gram-positive bacteria (Schempp et al., 1999b; Taponen et al., 2006). Nevertheless, antibacterial effects of hyperforin are only observed at high concentrations (Fiebich et al., 1999). Hyperforin did not exhibit any growth inhibitory effect against gram-negative bacteria, such as *Enterococcus faecalis*, *Escherichia coli* and *Pseudomonas aeruginosa*, or against *Candida albicans* (Schempp et al., 1999b). However, Hp essential oils, phloroglucinols, flavonoids, and tannins show antibacterial and antifungal activity (Saddiqe et al., 2010). These characteristics might alter intestinal microbiota acting as antibiotics, antimycotics and antiparasitics that deregulate intestinal balance (Sandler et al., 2000; Kantarcioglu et al., 2015), In an open study of 3250 patients, the most commonly reported side effects were gastrointestinal symptoms (0.6%) (Woelk et al., 1994), which could be related to the gut-brain-axis unbalance, altering neuronal regulation and disrupting central functioning (Mayer et al., 2015).

At first, attention was focused on hypericin as the constituent of St John's wort believed to be responsible for the herb's antidepressant effects. However, experimental (Chatterjee et al., 1998a, b) and clinical evidence (Laakmann et al., 1998) has now emerged to indicate that hyperforin is one of the major constituents required for antidepressant activity (Schrader, 2000). Nevertheless, Hp extracts show efficacy in the treatment of mild to moderate depression leading to its successful use as an antidepressant. The obtained results of a study with rats pregnant suggest lasting changes in the performances displayed in the CNS, depression and anxiety tests, indicating that the use of Hypericum during gestation could interfere with the behavioral development of the offspring reducing anxiety and depression when they become adults. Suggesting that these alterations are associated with the reprogramming of the brain regions related to changes in emotional reactivity (Campos et al., 2017).
Inhibition of monoamineoxidase (MAO) type A and B in rat brain mitochondria *in vitro* was described for hypericin (Suzuki et al, 1984; Rahimi et al., 2009; Linde, 2009). However, other studies have reported only weak or noMAO inhibition (Thiede and Walper, 1994; Yu, 2000) because its concentration was too low to explain the clinical effects (Butterweck, 2003). Hypericum extract demonstrated significant receptor affinity for adenosine, GABAa, GABAb, benzodiazepine (Cott, 1997). Hypericine inhibits the synaptosomal uptake of serotonin (5-hydroxytryptamine; 5-HT), dopamine and norepinephrine with approximately equal affinity and also led to a down-regulation of beta receptors and upregulation of 5-HT2 receptors in rat frontal cortex (Muller et al., 1997). Hyperforin has been shown to be an uptake inhibitorof 5-HT, dopamine, norepinephrine, GABA and L-glutamatein synaptosomal preparations (Chatterjee et al., 1998; Wonnemann et al., 2000), it has been reported that the mode of action of hyperforin in serotonin uptake inhibition seems to be associated with the elevation of free intracellular sodium ion concentrations (Singer et al., 1999) and that this maybe secondary to activation of the Na+/H+ exchange as a result of a decrease in intracellular pH (Singer et al., 2000).

## LAVENDER ESSENTIAL OIL (*L. angustifolia* Mill. - *L. hybrida, L. dentata* L. and *L. latifolia* Medik)

**Taxonomy:** Family: *Lamiaceae* - Genus: *Lavandula* - Species: *L. angustifolia - L. hybrida - L. dentata - L. latifolia*.

**Active compounds behavior modifiers:** linalool and linalyl acetate

**Effects on human behavior and animal models:** anxiolytic, anti-depressive, anti-stress, improves sleep quality.

*Lavandula* is a genus of well-known plants native to the lands surrounding the Mediterranean Sea and southern Europe through northern and eastern Africa and Middle Eastern countries to south Asia and have been used for centuries as an essential oil for therapeutic purposes (Barrett, 1996). Lavender essential oil (LEO) is a complex mixture mostly extracted from *Lavandula* species like *L. angustifolia. L. hybrida, L. dentata* and *L. latifolia*. LEO has been trialed to treat convulsion, pain, and central nervous system disorders such as anxiety, depression, stress, sleep disorders and vascular-brain diseases in many countries (Cavanagh and Wilkinson, 2002). Its major clinical benefits are concentrated in the central nervous system (Choi and Lee, 2012). Furthermore, it has antimicrobial activity against bacteria and fungi. Antispasmodic (Schulz et al., 1997) and anti-inflammatory effects have additionally been reported (Silva et al., 2015). *Lavandula* species contains more than 160 substances which major components are two monoterpenes; linalool and Linalyl acetate (Cavanagh and Wilkinson, 2002). Each of these constituents can vary significantly between species, in oils derived from different cultivars and be influenced by the distillation process (Mc Gimpsey and Porter, 1999). Several studies have been made to explain and understand the mechanism of these compounds in the nervous system (Hossein et al., 2013).

LEO may exert pharmacological properties via modulating the glutamate NMDA receptor in the cerebral cortex (Elizabetsky et al., 1995; Lopez et al.,

2017) as well as neurotoxicity induced by hydrogen peroxide and tert-butyl hydroperoxide (tBHP) (Kozics et al., 2017). Linalool is able to bind the serotonin transporter (SERT), contributing to its pharmacological properties. Besides that, it alters plasma adrenocorticotropic hormone (ACTH), catecholamine and gonadotropin levels in ovariectomised rats, these hormones have a role to play in the stress response and may explain any tension relieving properties of lavender (Yamada et al., 2005). Other authors such as Delaveau (1989) and Aoshima (2001) indicate an interaction with the GABA-A receptor, which is widely known to be involved in the etiology of anxiety. These compounds mentioned have shown multiple bioactivities on neuro-psychiatric disorders (Baron, 2015).

Authors have compared LEO with benzodiazepines due to its similar mechanism and results as an anxiolytic, having positive thoughts because of its lack of side effects (Bradley et al., 2007).Choi et al., studied in 2013 the effects of aromatherapy, showing a decrease in anxiety and an improvement in sleep quality with no significant differences in systolic and diastolic blood pressure. Although, other studies show that inhaled aromatherapy is not the only way to exploit all its properties. In a randomized, double-blind controlled trial in 2010, investigators used an oral LEO capsule to prove it´s anxiolytic efficacy. Their results revealed efficacy and safety for the relief of anxiety disorder and anxiety related disturbed sleep (Kaspera et al., 2010). Because of its relaxing, antioxidant and stress reliever properties, it has been used in therapies for Autism Spectrum Disorder and ADHD (Autism Parenting Magazine, 2016).

This essential oil can be used in massages to treat muscular pain, neck pain (Yip and Tse, 2006), Low back pain (Yip and Tse, 2004), and menstrual pain (Marzouk *et al*., 2013). In an experimental study, 28 patients with neck pain had manual acupressure with lavender oil. After a month of treatment the manual acupressure group had 23% reduced pain intensity compared to the control group (Yip and Tse, 2006). Essential oils have been so common and popular that it has even being used in baths with positive findings (Morris, 2002).

## CANNABIS ESSENTIAL OIL (*Cannabis sativa* L., *Cannabis indica* Lan. and *Cannabis ruderalis* Janish.)

**Taxonomy:** Family: *Cannabaceae* - Genus: *Cannabis* - Species: *C. sativa – C. indica – C. ruderalis.*

**Active compounds behavior modifiers:** Δ9-tetrahydrocannabinol (THC), cannabidiol (CBD) and others minors.

**Effects on human behavior and animal models:** euphoria, a feeling of relaxation, and intensification of ordinary sensory experiences, anxiolytic, sedative, anti-schizophrenic

*Cannabis* is a genus of plants with flowers that can be cultivate all around the world if its conditions are adequate. This plant has a long history in traditional medicine of China, Europe, Greeks and India (Kuddus et al., 2013). Used since ancient times to alleviate chronic pain derived from diseases. It was a very popular drug for consumption but eventually derailed by political factors in the United States (US) consisting of propagandas. Therefore, a misguided stigma of Cannabis was created in 1930s, associating psychosis, mental deterioration, addiction, and violent crimes to marijuana use (Whiting *et al*., 2015). Nowadays, there are countries in South America, Europe and some states of United States of America (among others) that legalized its consumption and with this, many studies has been made to analyze its benefits. There are 3 primary cannabis species: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. These, have more than 400 compounds, although, there is two cannabinoids that are mainly studied; Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (D'souza and Ranganathan, 2015). Cannabinoids are a set of psychoactive compounds present in a resin secreted from the leaves and blossomed buds of Cannabis; preparations of the plant can be in the form of hachish, marijuana and commercial products (González et al., 2002).

Cannabis potency is influenced by genetics, growing conditions (especially light), harvest time, the part of the plant used, drying, storing and processing (Potter, 2014). Cannabis can be administrated by inhalation (smoking), ocular, dermic, intravenous, oral and rectal for therapeutic reasons (Pinar-Sueiroa et al., 2011). Smoking is the most common way to be used for recreational purposes (Ribeiro and Philip, 2016). When marihuana is inhaled, subjects experience euphoria, a feeling of relaxation, and intensification of ordinary sensory experiences (Rodriguez, 2012). Chronic consumption can result in tolerance, dependence, withdrawal syndrome, cognitive deterioration, and increased risk of psychiatric illnesses (Budney et al., 2004).

When Cannabis preparations are consumed in the form of cigarettes it is absorbed by the lungs. The entrance of THC in blood and the subsequent distribution in tissues are very fast. Ingestion of oral cannabinoids results in initially lower THC plasma levels than taken by inhalation (González et al., 2002). Its bioavailability is reduced orally because of its sensitivity to acidity of gastric juice, liver and intestinal metabolism, and its access to enterohepatic circulation (Agurell et al., 1986). Therefore, it is

necessary to ingest a greater amount to get the same physiological effect as for the respiratory one.

The discovery of an endogenous cannabinoid system renewed medical interest in marijuana, and data from recent years indicate that the endocannabinoid system regulates the function of various types of synapses (Aggarwal, 2013) including inflammation, appetite regulation, neural development, immune function, cardiovascular function, synaptic plasticity and learning, pain, memory, psychiatric disease, psychomotor behavior, regulation of stress, emotion, among others (Howlett, 2004; Rodriguez et al., 2005; Greco et al., 2010; Serrano and Parsons, 2011; Aggarwal, 2013). The endocannabinoid system consists of the cannabinoid 1 (CB1) and 2 (CB2) receptors, the endogenous cannabinoid receptor ligands (endogenous cannabinoids) N-arachidonoylethanolamine (anandamide, or AEA) and 2-arachidonoylglycerol (2-AG), as well as their degrading enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase, respectively (Serrano and Parsons, 2011; Battista et al., 2012). CB1 is a G protein wich has a presynaptical function in the central nervous system. CB2 receptors are thought to be linked to immune function and are concentrated in peripheral tissues (Pacher et al., 2006). Δ9-Tetrahydrocannabinol (THC), known as the main psychoactive component of Cannabis, exerts its effects through the endocannabinoid system, by acting on CB1, CB2 receptors (Turna et al., 2017) and seems to possess antiseizure activity (Schulz et al., 1997).

In the other hand, Cannabidiol (CBD) is a phytocannabinoid which lacks the significant psychoactive, or "high-inducing," effects of THC but has demonstrated anti-inflammatory, analgesic, anticonvulsant, and anxiolytic properties (Blessing et al., 2015). Although the mechanism behind these effects remains unclear, the function of CBD may be related to its action as an antagonist/inverse agonist of CB1 receptors (Thomas et al., 2007) or as a positive allosteric modulator of 5HT1A receptors (Rock et al., 2012). An attribute of CBD is that possess neuroprotective and anti-inflammatory effects (Hampson et al., 2000). A preclinical study revealed that tetrahydrocannabinol (THC) and cannabidiol (CBD) clearly have anticonvulsant properties in animal models of acute seizures and epilepsy (Wallace et al., 2002; Jones et al., 2010).

High CBD content Cannabis report only minor side effects, such as somnolence or fatigue, and only a few patients withdrew treatment due to side effects (Porter and Jacobson, 2013; Press et al., 2015). On the other hand, THC has significant addictive potential. Even though it has been demonstrated the negative side effects of high dosis of THC (anxiety, dysphoria, panic and paranoia, especially in new users (Gowing et al., 1998) some authors have studied the benefits that provides CBD with THC. They came to the conclusion of that when administered together, CBD may also have the ability to reverse the unwanted and anxiogenic effects of THC by antagonizing THC pharmacodynamically (Bhattacharyya et al., 2010; Fusar-Poli et al., 2010). Treatment of neurologycal disorders, are studied on the field of endocanabinoid system, due to an abundance of CB1 receptors in the striatum, a component of the Cortico-Striato-Thalamo-Cortical circuit which is believed to be dysfunctional in Obsessive Compulsive Disorder (OCD) (Schindler et al., 2008) . Many synapses in this region are also glutamatergic and glutamate hyperactivity is believed to be one mechanism that underlies OCD symptomology (Wu et al., 2012). Cannabinoids inhibit glutamate release in the central nervous system (Gomes et al., 2011), therefore reduces motor activity having positive effects in the treatment of OCD, Trichotillomania and Tourette's syndrome (TS) (Grant et al., 2011).

To summarize other medicinal benefits, it has been showed positive results treating conditions like Autism spectrum disorder (Kurz and Blass K, 2010), Gastrointestinal disorders (irritable bowel syndrome, inflammatory bowel disease, pain (Kimball et al., 2010; Naftali et al., 2013), Parkinson's disease (Muller-Vahl et al., 1999), depression and anxiety (Petersen, 1976), as well as an antidepressant (El-Alfy et al., 2010) and analgesic (Elikottil et al., 2009). Clendinning in London was one of the first Western physicians to treat migraine with Cannabis in the 1840s, since then, usage of marihuana for migraines and headaches have been described with positive findings (Clendinning, 1843; Greene, 1872; Osler and McCrae, 1915; McGeeney, 2013).

The dosis in those studies were suministrated by inhalation and suppositories. Cannabis has great therapeutic properties that can be harnessed to the maximum if they are well administered and controlled. However, because of inconsistencies in amount of dosage across studies, there is no clear conclusion on whether there exists a safe amount of *Cannabis* use. Further studies are needed in order to standardize these variables for each disease and disorder.

**BERGAMOT ESSENTIAL OIL (*Citrus bergamia* Risso & Poit.)**

**Taxonomy:** Family: *Rutaceae* - Subfamily: *Citroideae* - Tribe: *Citreae* - Genus: *Citrus* - Specie: *C. bergamia.*

**Active compounds behavior modifiers:** linalool, linalyl acetate and Limonene.

**Effects on human behavior and animal models:** anxiolytic/relaxation effects, anti-stress

*Citrus bergamia* is a fragrant fruit with green color similar to the lime, originates from the Mediterranean region, particularly from southern Italy and Greece. Genetics had shown that it's probably a hybrid between *Citrus limetta* and *Citrus aurantium*. Bergamot can be used to make perfumes, food, cosmetics, and aromatherapy. In fact, Bergamot oil (BEO) is commonly used against psychological stress and anxiety in aromatherapy, but there is also some interesting ways like it affects the state of mood, anticancer activity, and inhibition of oxydative stress. All those particularities are due to the component of the plant. The most abundant compounds are the monoterpene hydrocarbons d-limonene (25.62%–53.19% of the whole essential oil), the monoterpene ester, linalyl acetate (15.61%–40.37%), and the monoterpene alcohol, linalool (1.75%–20.26%) (Melliou et al, 2009).

According to recent research in a combination of fields, such as phytochemical analysis, pharmacology, and psychology, a variety of volatile oils have specific neuropharmacological effects. The individual volatile oil compounds are detected by the olfactory nerve on the back of the nasal cavity, which carries more than 1,000 kinds of receptors and is directly connected via the intracranial olfactory bulb to the limbic system in the hypothalamus and thus to the autonomic nervous system. Accordingly, effects on the endocrine and immune systems have been demonstrated. Furthermore, volatile oil components inhaled during aromatherapy can pass from the alveoli into the capillary blood vessels. Even if rubbed into the skin, they can enter through the subcutaneous tissue into the capillaries and pass the blood-brain barrier with the bloodstream, thus affecting the entire central nervous system. (Watanabe and Kimura, 2015). Bergamot oil seems to have effects on hypothalamus pituitary adrenocortical axis, by reducing anxiety and stress. (Rombolà et al, 2017).

When a stressor reaches the cerebral cortex, adrenocorticotropic hormone (ACTH) is released from the hypothalamus stimulating the secretion of cortisol from the adrenal cortex. Based on this knowledge, a recent study have used salivary cortisol of 41 healthy females (CS) levels as an indicator for stress reduction in previous research projects, demonstrating that during emotional improvement after relaxation cortisol levels are also reduced (Watanabe and Kimura, 2015). They also measured the heart rate frequency to see the activity of the parasympathetic nervous system. Results have shown that it really increase the parasympathetic system and decrease the CS level, that can be linked with a stress reduction, and that the effects depend of the time between the inhalation and the effect on the brain. That could be increased by water et volatile oil mix, to ameliorate the physiological and psychological effect of the BEO. Another study show that liposomal BEO can be used to limit the use of toxic solubilizing agents especially to improve the anticancer activity of the oil on human neuroblastoma cells but we could expect a similar effect with liposomal BEO on behavior troubles (Celia et al, 2013).

According to others studies (Rombolà et al, 2017) it seems to be an interesting way to treat some disorders of the behavior, especially while anxiolytic dose of benzodiazepine (DZP) seems to affect the vigilance of the rats, unlike BEO which allows to the rats some alert behaviors. In fact, spontaneous behavior is reflected in the electroencephalographic (EEG) activity and it is known that hippocampal rhythmic slow activity and cortical low voltage fast activity dominate the EEG during "voluntary movements" but not during sedation. Incidentally, previous results indicated that systemic doses of BEO increase alpha EEG frequency correlate to relaxation, and beta brainwave activity, associated with being alert and awake. A different EEG pattern is observed with DZP that decreases delta and alpha and increases beta-3/gamma activity. Therefore, both behavioral and EEG data seem to support the hypothesis that other neurotransmitter systems, in addition to the GABAergic, could be likely involved in the anxiolytic/relaxant effect of bergamot oil (Rombolà et al, 2017). Aromatherapy with bergamot oil seems to be promising in treating behavior disorders all the more when chronic benzodiazepines use induces drowsiness, lethargy, dizziness, vertigo, sedation, tolerance and dependence (Tampi et al, 2014).

Another interesting way of use of Bergamot oil is to restore opioids analgesic efficacy, with the bergamot polyphenolics fraction (BPF) that allow an antioxidant function. In fact, mice treated by several morphine intakes develop an analgesic tolerance. It was observed that repeated administration of morphine for several consecutive days produced tolerance to the opioid and an increase in superoxide formation in the L4-L5 portion of the mice spinal cord. BPF co-administration was able to inhibit morphine tolerance reducing O2- chronic morphine-induced increase. The increase of superoxide anion leads to the oxidation of glutamine-synthetase which normally allow to the synapse to reduce the stimulation by reducing glutamate level. The antioxidant effect of BPF seems to restore the normal function and make more effective the long term use of morphine. It could be an interesting way for the use of BEO in behavior disorders because of reducing the glutamate level, neurotransmitter which is responsible

of excitation in the nervous system (Lauro et al., 2016).

## OLIVE ESSENTIAL OIL (*Olea europea* L.)

**Taxonomy:** Family: *Oleaceae* - Genus: *Olea* - Specie: *O. eurepea.*

**Active compounds behavior modifiers:** oleuropein and hydroxytyrosol (probably).

**Effects on human behavior and animal models:** anxiolytic and antidepressant effects

Olive is used throughout the world especially in the Mediterranean region. It is full of nutriments and vitamins. It has the most delicate flavor and antioxidant benefit (Aguilera & Ramirez-Tortosa, 2001). Olive oil is rich in monounsaturated fatty acids (MUFAs) and has excellent health benefits (Alarcón et al, 2001). It is composed mainly of mixed triglyceride esters of oleic acid, palmitic acid, and other fatty acids, along with the traces of squalene (up to 0.7%) and sterols (about 0.2%; phytosterol & tocosterols). It also contains group of antioxidants that are esters of tyrosol and hydroxytyrosols, including oleocanthal, oleuropein, vitamin E and carotenoids. Oleuropein is a chemical that prevents the oxidation of LDL (low-density lipoproteins) particles (Coni et al., 2000). It has been reported that omega-3 fatty acid, docosahexaenoic acid (DHA), plays an adaptive role during stress and shows a significant reduction in perceived stress (Bradbury et al., 2004) by increasing secretion of adrenal corticosterone in rats loaded with single repetitive stress (Condo et al., 2000).

It must be underlined that repeated administration of extra-virgin olive oil produces anxiolytic and antidepressant effects via neurochemical alterations in brain 5-HT,DA,and their metabolites (Perveen et al., 2013) .Role of 5-HT in anxiety is well documented. Increased 5-HT produces anxiogenic effect while decreased level of 5-HT produces anxiolytic effect (Gupta and Chopra, 2010). It has been observed that repeated administration of extra-virgin olive oil produce significant antidepressant effects as the struggling time of rats taking olive oil was significantly increased as compared to control rats. (Perveen et al., 2013) This indicates that olive oil has great potential to reduce depression which may be due to presence of linoleic acid; a polyunsaturated omega-3 fatty acid that makes up 1.5% of extra-virgin olive oil (Sirtori et al., 2007).

Morever, data on bioavailability indicate that, in spite of extensive metabolism by microbiota and physiological modifications by the organism, plant, notably olive, polyphenols are, at least in part, absorbed and distributed to body organs, including the brain, before excretion (Fiorella Casamenti and Stefani, 2016).

The most widespread neurodegenerative conditions in the population are associated with ageing and comprise severe pathologies, such as Alzheimer Disease (AD) and Parkinson Disease (PD) that compromise memory, cognition, sociality, gait, and motor coordination and interfere heavily with the everyday life. These, and other neurodegenerative diseases, both in the sporadic and, when present, in the familial forms, are characterized by the presence of intracellular and/or extracellular (amyloid plaques) deposits of an intricate mesh of fibrillar aggregates arising from the aberrant polymerization of specific peptides/proteins, typically Aβ peptides and tau protein in AD, tau protein in other tauopathies (e.g. frontotemporal dementia), α-synuclein in PD, huntingtin in Huntington disease and various ataxins in several ataxias (Selkoe, 2003).

At micromolar concentrations, Olive Leaf Extract (OLE) has been shown to interfere in vitro with amyloid aggregation of the Aβ 42 peptide (Rigacci et al., 2011), amylin (Rigacci et al., 2010), and transthyretin (Leri et al., 2016) ; moreover, oleuropein, OLE, and hydroxytyrosol (HT) have been reported to hinder in vitro amyloid aggregation of tau protein into fibrillary tangles. A similar behavior has also been reported for oleocanthal; it was shown to interact covalently with tau inducing conformational modifications that interfered with protein aggregation. Oleocanthal was also reported to interfere with Aβ aggregation favoring the growth of oligomers with altered structure, modified immunoreactivity, and reduced binding to synapses and synaptotoxicity (Pitt et al., 2009). Olive polyphenols can also interfere indirectly with Aβ40/42 aggregation.

## BLACK CUMIN ESSENTIAL OIL (*Nigella sativa* L.)

**Taxonomy:** Family: *Ranunculaceae* - Subfamily: *Ranunculoideae* - Tribe: *Nigelleae* - Genus: *Nigella*- Specie: *N. sativa.*

**Active compounds behavior modifiers:** thymoquinone.

**Effects on human behavior and animal models:** anxiolytic and antidepressant effects

*Nigella Sativa (NS)* also known as Black Cumin is an annual flowering plant native to south and southwest Asia (Botanical Society of Britain and Ireland, 2007). The seeds of the plant have a long history of use in different frameworks of medicines and food. In Islamic literature, it is considered as one of the

greatest forms of therapeutics (Aftab Ahmad, 2013). It has been widely used to treat nervous system diseases such as memory impairment, epilepsy, neurotoxicity, pain, etc. Additionally, this is uncovered that the majority of therapeutic properties of this plant are due to the presence of thymoquinone (TQ) which is a major bioactive component of the essential oil. Pharmacological studies have been done to evaluate the effects of NS on the central nervous system (CNS) (Hosseinzadeh, 2004). The present review is an effort to provide a detailed scientific literature survey about pharmacological activities of the plant on nervous system. The essential oil contain 48 compounds, the most interesting psychoactive compound is Thymoquinone (TQ).

Concerning anxiety and depression, a study where was following four weeks of daily administration of NS oil (NSO) to mices, it showed an increment in open field activity. The animals also had a better performance when tested in elevated plus maze. An oral administration of NSO raised brain levels of 5-hydroxytryptamine (5-HT), but the levels of brain hydroxyindole acetic acid (5-HIAA) significantly reduced. Likewise, brain and plasma levels of tryptophan increased after repeated oral administration of NSO (Perveen, 2009). TQ has also shown an anti-anxiety-like effect in mice through modulation of γ-aminobutyric acid (GABA) and nitric oxide (NO) levels in the brain or plasma (Gilmore, 2011). In another study, mice were subjected to 6h immobilization in order to experience stressed conditions and the role of GABAergic and nitriergic modulation in the anti-anxiety effect of TQ has been investigated. TQ (10 and 20 mg/kg) produced significant anti-anxiety effects in unstressed mice without altering nitrite levels, but only the higher dose (20 mg/kg) of TQ increased the GABA content in unstressed mice.

In stressed mice, TQ (20 mg/kg) showed anxiolytic effects with a significant reduction in plasma nitrite and brain GABA content. Pre-treatment with methylene blue improved the anti-anxiety effect of TQ in both unstressed and stressed mice. Hence, an association between NO-cGMP and GABAergic pathways in the anxiolytic-like activity of TQ has been proposed (Gilhotra and Dhingra, 2011). The results of the previous study also showed that injection of 200 and 400 mg/kg of hydro-alcoholic extract of NS prevented lipopolysaccharide-induced depression-like behavior in rats (Hosseini et al., 2012), which confirmed the anti-depressive effects of the plant and suggested that the effects might be due to its anti-inflammatory properties. It is also concluded that NS, NSO and TQ improve anxiety and depression. It seems that the effects are related to the effects of GABA, NO and 5-HT. It has also been reported that administration of TQ (5 mg/kg/day, orally) 5 days before ischemia and continuing it during the reperfusion time, prevented brain damage in a model of transient forebrain ischemia in the rat hippocampus (Al-Majed et al., 2006). The study also showed that TQ stimulated resistance to oxidative stress by decreasing the elevated levels of MDA, glutathione (GSH) contents, CAT and SOD (Al-Majed et al., 2006).

A protective effect for TQ was also reported in 1-methyl-4- phenylpyridinium (MPP)-treated primary dopaminergic cultures and a primary Parkinson's disease model involving rotenone and neuroinflammatory mechanisms. In this study, rotenone, a well-known insecticide, following both short (20 nmole on day 10 i.v. for 48 h) and long-term (1 nmole on day 6 i.v. for 6 consecutive days) treatment reduced the number of tyrosine hydroxylase immunoreactive which was prevented by TQ (Radad et al., 2009).

## VALERIAN ESSENTIAL OIL (*Valeriana officinalis* L.)

**Taxonomy:** Family: *Caprifoliaceae* - Subfamily: *Valerianoideae* - Genus: *Valeriana* - Specie: *V. officinalis.*

**Active compounds behavior modifiers:** valerenic acid, valerenal.

**Effects on human behavior and animal models:** anti-depressant, anxiolytic, sedative effects, improves sleep quality and decreases sleep latency.

The root of *Valerian officinalis*, a pink-flowered perennial that grows wild in temperate areas of the Americas and Eurasia, has been a popular calming and sleep-promoting agent for centuries. German health officials have approved valerian for use as a mild sedative and sleep aid, based on several European clinical trials that demonstrate these effects (Kamm-Kohl et al., 1984). Because of valerian's historical use as a sedative, antiseptic, anticonvulsant, migraine treatment, and pain reliever, most basic science research has been directed at the interaction of valerian constituents with the GABA receptor (Boullata et al., 2000). Many studies remain inconclusive and all require clinical validation. The mechanism of action of valerian in general, and as a mild sedative in particular, has not been fully elucidated. However, some of the GABA-analogs, particularly valerenic acids as components of the essential oil along with other semivolatile sesquiterpenoids, generally are believed to have some affinity for the GABAA receptor, a class of receptors on which benzodiazepines are known to act. (Holzl, 1989) (Mennini et al., 1993) Valeric acid, which is responsible for the typical odor of mostly older

valerian roots, does not have any sedative properties. Valeric acid is related to valproic acid, a widely prescribed anticonvulsant; valproic acid is a derivative of valeric acid.

Valerian also contains isovaltrate, which has been shown to be an inverse agonist for adenosine A1 receptor sites. This action likely does not contribute to the herb's possible sedative effects, which would be expected from an agonist, rather than an inverse agonist, at this particular binding site. Hydrophilic extractions of the herb commonly sold over the counter, however, probably do not contain significant amounts of isovaltrate (Lacher et al., 2007). Valerenic acid in valerian stimulates serotonin receptors as a partial agonist (Patočka, 2010) including 5-HT5A which is implicated in the sleep-wake cycle (Dietz et al., 2005). In 2 randomized sutides, (Leatherwood, 1982) (Lindahl and lindwell, 1989); blind, and placebo-controlled crossover trials (n=27 and n=128), valerian (400-450 mg before bedtime) resulted in significantly improved sleep quality and decreased sleep latency, with no residual sedation in the morning. *In vitro*, constituents of valerian mediate the release of -aminobutyric acid (Leuschner et al., 1993) and bind the same receptors as benzodiazepines, but with less affinity and milder clinical effects. (Mennini et al., 1993) Habituation or addictions have not been reported.

Anxiolytic or Sedative/Hypnotic activity: In mice, intraperitoneal injections of valerenic acid, valerenal and whole herb extracts produced significant sedation, ataxia and anticonvulsant effects (Veith et al., 1986). Intraperitoneal injections of 100 mg/kg had sedative effects as strong as barbiturates; doses of 400 mg/kg led to death. In comparison with diazepam and chlorpromazine, valerian extract had weak anticonvulsive properties. Valerian root extract (Valdispert) reduced motility and increased thiopental-induced and pentobarbital-induced sleeping time.

Even the aroma of valerian root exerted sedative effects in mice (Buchbauer et al., 1992). Other Neurologic activity: Unlike diazepam, valerian did not affect spontaneous ambulation and rearing or approach-avoidance conflict in mice in a water-lick conflict test. On the other hand, valerian and imipramine significantly inhibited immobility induced by a forced swimming test in rats and significantly reversed reserpine-induced hypothermia in mice, leading researchers to conclude that valerian may be a useful antidepressant (Sakamoto et al., 1992).

In the annex (Table 1) shows studies conducted with other essential oils of other plants not addressed in this review.

## CONCLUSIONS

The use of essential oils in their various forms of administration either inhaled (aromatherapy), topical application or ingested emerges as an alternative tool in the conventional therapy of many problems associated with mood, behavior and sleep disorders. The studies mentioned in this review have shown the efficacy and stability of different essential oils. It is important to establish the optimal dosage of the EO to use it as an adjuvant of treatment for different disorders. Many of these plants share the property of having anxiolytic effects, being anxiety the core symptom observed in emotional problems, developmental disorders such as ADHD, ASD, psychiatric disorder such as schizophrenia, neurodegenerative diseases, neoplasms, metabolic diseases and even on people with typical development.

## REFERENCES

Abuznait, H.A., Qosa, H., Busnena, B.A., El Sayed, K.A., Kaddoumi, A. 2013. Olive-oil-derived oleocanthal enhances βamyloid clearance as a potential neuroprotective mechanism against Alzheimer's disease: in vitro and in vivo studies. ACS Chem Neurosci. 4: 973–982. DOI: 10.1021/cn400024q

Addae, J.I., Pingal, R., Walkins, K., Cruickshank, R., Youssef, F., Nayak, S.B. 2017. Effects of Jasminum multiflorum leaf extract on rodent models of epilepsy, motor coordination and anxiety. Epilepsy Res.131: 58-63. DOI: 10.1016/j.eplepsyres.2017.02.012

Aggarwal, S.K. 2013. Cannabinergic pain medicine: A concise clinical primer and survey of randomized-controlled trial results. Clin J Pain. 29:162-171. DOI: 10.1097/AJP.0b013e31824c5e4c.

Aguilera, C.M., Ramírez-Tortosa, M.C., Mesa, D., Gil, A. 2001. Protective effects of monounsaturated fatty acids and polyunsaturated fatty acids in the development of cardiovascular disease. Nutricion Hospitalaria. 16(3):78–91.

Agurell, S., Halldin, M., Lindgren, J., Ohlsson, A., Widman, M., Gillespie, H., Hollister, L.1986. Pharmacokinetics and metabolism of delta-9-THC and other cannabinoids with emphasis on man. Pharmacol. Rev. 38: 21-42.

Alarcón de la Lastra, C., Barranco, M.D., Motilva, V., Herrerías, J.M. 2001. Mediterranean diet and health: biological importance of olive oil. CurrentPharmaceuticalDesign, 7 (10): 933–950.

Alhebshi, A.H., Gotoh, M., Suzuki, I. 2013. Thymoquinone protects cultured rat primary

neurons against amyloid beta-induced neurotoxicity. Biochem Biophys Res Commun. 19;433(4): 362-367. DOI: 10.1016/j.bbrc.2012.11.139.

Ali, S.S., Abd El Wahab, M.G., Ayuob, N.N., Suliaman, M. 2017. The antidepressant-like effect of Ocimum basilicum in an animal model of depression. Biotech Histochem. 11:1-12. DOI: 10.1080/10520295.2017.1323276

Al-Majed, A.A., Al-Omar, F.A., Nagi, M.N. 2006. Neuroprotective effects of thymoquinone against transient forebrain ischemia in the rat hippocampus. Eur J Pharmacol. 14; 543(1-3): 40-7. DOI: 10.1016/j.ejphar.2006.05.046

Aoshima, H., Hossain, S.J., Hamamoto, K., Yokoyama, T., Yamada, M., Shingai, R. 2001. Kinetic analyses of alcohol-induced potentiation of the response of GABA (A) receptors composed of alpha (1) and beta (1) subunits. J Biochem. 130(5):703-9.

Autism Parenting Magazine. 2016. Best Essential Oils for Autism and ADHD – The Ultimate Guide. Available in: https://www.autismparentingmagazine.com/essential-oils-for-autism-adhd-add/ Septiembre2017

Ayuga, C., Rebuelta, M. 1986. A comparative study of phenolicacids of HypericumcaprifoliumBoiss and Hypericumperforatum L.An. Real Acad. Farm. 52:723-728.

Barnes, J., Linda, A., Anderson, J., Phillipson, D. 2001. St John's wort (Hypericumperforatum L.): a review of its chemistry, pharmacology and clinical properties. Journal of Pharmacy and Pharmacology.53: 583-600

Baron, E.P. 2015. Comprehensive Review of Medicinal Marijuana, Cannabinoids, and Therapeutic Implications in Medicine and Headache: What a Long Strange Trip It's Been. Headache. 55(6):885-916. DOI: 10.1111/head.12570

Barrett, P. 1996. Growing and using lavender. Storey Country wisdom bulletin. US. Story Publishing LLC

Battista, N., Di Tommaso, M., Bari, M., Maccarrone, M. 2012. The endocannabinoid system: An overview. Front Behav Neurosci. 6:1-7. DOI: 10.3389/fnbeh.2012.00009

Beheshti, F., Hosseini, M., Shafei, M.N., Soukhtanloo, M., Ghasemi, S., Vafaee, F., Zarepoor, L. 2014. The effects of Nigella sativa extract on hypothyroidism-associated learning and memory impairment during neonatal and juvenile growth in rats. Nutr Neurosci. 20.(1) 49-59. DOI: 10.1179/1476830514Y.0000000144

Beheshti, F., Hosseini, M., Vafaee, F., Shafei,M.N., Soukhtanloo, M. 2015. Feeding of Nigella sativa during neonatal and juvenile growth improves learning and memory of rats. J Tradit Complement Med. 6. (2):146-152. DOI: 10.1016/j.jtcme.2014.11.039

Bennett, D.A., Phun, L. Jr., Polk, J.F., Voglino, S.A., Zlotnik, V., Raffa, R.B. 1998. Neuropharmacology of St. John's wort (Hypericum). Ann Pharmacother. 32: 1201–1208.

Berghöfer, R., Hölzl, J. 1987.Biflavonoids in Hypericumperforatum;Part 1. Isolation of 13, II8-biapigenin. Planta Med. 53: 216-217.

Bhattacharyya, S., Morrison, P., Fusar-Poli, Martin-Santos, R., Borgwardt, S., Winton-Brown, T. and Mehta, M. 2010. Opposite effects of Δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology. 35(3): 764–774.

Biber, A., Fischer, H., Römer, A., Chatterjee, S.S. 1998. Oral bioavailability of hyperforin from Hypericum extracts in rats and human volunteers. Pharmacopsychiatry. 31: 36–43.

Bielekova, B., Martin, R. 2004. Development of biomarkers in multiple sclerosis. Brain. 127. (7):1463–1478.DOI: 10.1093/brain/awh176

Bisset, N.G. 1994. Herbal Drugs and Phytopharmaceuticals (Wichtl, M. editor, German edition). Stuttgart: Medpharm. Scientific Publishers, CRC Press, Stuttgart.Germany

Blessing, E. M., Steenkamp, M., Manzanares, J., Marmar, C. 2015. Cannabidiol as a potential treatment for anxiety disorders. Neurotherapeutics. 12: 825–836.

Bondia-Pons, I ., Schroder, H ., Covas, M.I., Castellote, AI., Kaikkonen, J., Poulsen, H.E., Gaddi, A.V., Machowetz, A., Kiesewetter, H., López-Sabater, M.C. .2007. Moderate consumption of olive oil by healthy european men reduces systolic blood pressure in non-mediterranean participants. JournalofNutrition.137(1):84–87. DOI: 10.1093/jn/137.1.84.

Boullata, J.I., Nace, A.M. 2000. Safety Issues with Herbal Medicine: Common Herbal Medicines.Pharmacotherapy. 20(3):267-279. DOI: 10.1592/phco.20.4.257.34886.

Bradbury, J., Myers, S.O., Oliver, C. 2004. An adaptogenic role for omega-3fattyacidsinstress; arandomised placebo controlled double blind intervention study.NutritionJournal. 3:20. DOI: 10.1186/1475-2891-3-20

Bradley, B., Starkey, N., Browna, S., Lea, R. 2007. Anxiolytic effects of Lavandula angustifolia odour on the Mongolian gerbil elevated plus

maze. Journal of Ethnopharmacology. 111: 517–525.

Brochmoller, J., Rheum,T., Bauer, S., Kerb, R., Hubner, W.D., Roots , I.1997. Hypericin and pseudohypericin: pharmacokinetics andeffects on photosensitivity in humans. Pharmacopsychiatry 30: 94–101.

Brondz, I., Greybrok, T., Aasen, A. J. 1983. N-Alkanes of Hypericumperforatum: A revision. Phytochemistry 22: 295-296.

Buchbauer, G., Jager, W., Jirovetz, L., Meyer, F., Dietrich, H. 1992.Effects of valerian root oil, borneol, isoborneol, bornyl acetate and isobornyl acetate on the motility of laboratory animals (mice) after inhalation. Pharmazie. 47(8):620-622.

Budney, A., Hughes, J., Moore, B., Vandrey, R. 2004. Review of the validity of cannabis withdrawal syndrome. American Journal of Psychiatry.161(11): 1967–1977.

Butterweck, V. 2003. Mechanism of action of St John's wort in depression: what is known? CNS Drugs.17: 539–562.

Butterweck, V., Schmidt, M. 2007. St. John's wort: role of active compounds for its mechanism of action and efficacy. WienMed Wochenschr. 157: 356–361.DOI: 10.1007/s10354-007-0440-8

Campos L., Vieira, V.,Silva, L., Jasmin, J.,Guerra, M., Peters, V., Cássia da Silveira e Sá, R.2017. Rats treated with Hypericumperforatum during pregnancy generate offspring with behavioral changes in adulthood. Revista Brasileira de Farmacognosia. 27:361–368.DOI: 10.1016/j.bjp.2017.01.004.

Can, O.D., Ozkay, U.D. 2012. Effects of Hypericummontbretti extract on the central nervous system and involvement of GABA (A)/benzodiazepine receptors in its pharmacological activity. Phytother Res 26: 1695–1700. DOI: 10.1002/ptr.4629

Can, Ö.D., Öztürk, Y., Öztürk, N., Sagratini, G., Ricciutelli, M., Vittori, S., Maggi, F. 2011. Effects of treatment with St. John's wort on blood glucose levels and pain perceptions of streptozotocin-diabetic rats. Fitoterapia 82: 576–584. DOI: 10.1016/j.fitote.2011.01.008

Capasso, F., Gaginella, T.S., Grandolini, G., Izzo, A.A. 2003. Phytotherapy: A Quick Reference to Herbal Medicine. SpringerVerlag: Berlin.

Cárdenas ,J., Reyes-Pérez, V., Hernández-Navarro, M.D., Dorantes-Barrón ,A.M., Almazán, S.,Estrada-Reyes, R. 2017. Anxiolytic- and antidepressant-like effects of an aqueous extract of Tanacetum parthenium L. Schultz-Bip (Asteraceae) in mice. J Ethnopharmacol. 22; 200:22-30. DOI: 10.1016/j.jep.2017.02.023.

Casamenti, F., Massimo, S. 2016. Olive polyphenols: New promising agents to combat aging-associated neurodegeneration, Expert Review of Neurotherapeutics.17 (4): 345-358. DOI: 10.1080/14737175.2017.1245617

Cavanagh, H and Wilkinson, J. 2002. Biological activities of lavender essential oil. Phytotherapy Research. 16(4): 301–308. DOI: 10.1002/ptr.1103.

Chatterjee, S., Bhattacharya, S., Wonnemann, M., Singer, A., Muller, W. E. 1998. Hyperforin as a possible antidepressant component of hypericum extracts. Life Sci. 63: 499-510.

Chen, X.W., Serag, E.S., Sneed, K.B., Liang, J., Chew, H., Pan, S.Y., Zhou, S.F. 2011. Clinical herbal interactions with conventional drugs: from molecules to maladies.Curr Mel Chem 8: 4836–4850.

Chevalier, A. 1996. The encyclopedia of medicinal plant: a practical reference guide to over 550 key herbs and their medicinal uses. London: Dorling Kindersley. 171p.

Choi, E., Lee, K. 2012. Effects of aroma inhalation on blood pressure, pulse rate, sleep, stress, and anxiety in patients with essential hypertension. J Korean Biol Nurs Sci 14:41–48.DOI:10.7586/jkbns.2012.14.1.41.

Celia, C., Trapasso, E., Locatelli, M., Navarra, M., Ventura, C.A., Wolfram, J., Carafa, M., Morittu, V.M., Britti, D., Di, Marzio, L., Paolino, D. 2013. Anticancer activity of liposomal bergamot essential oil (BEO) on human neuroblastoma cells. Elsevier, Colloïds and Surfaces B. Biointerfaces. 112:548-553. DOI: 10.1016/j.colsurfb.2013.09.017

Clendinning, J. 1843. Observations on the medical properties of the cannabis sativa of India. Med Chir Trans. 26:188-210.

Coni, E., Di Benedetto,R., Di Pasquale, M., Masella R., Modesti, D., Mattei, R., Carlini, E.A. 2000. Protective effect of oleuropein,and olive oil biophenol, on low density lipoprotein oxidizabilityinrabbits, Lipids,35(1).45–54

Cott, J. M. 1997.In vitro receptor binding and enzyme inhibition by Hypericumperforatumextract. Pharmacopsychiatry. 30(Suppl): 108-112.

Covas, M.I. 2007.Olive oil and the cardiovascular system. Pharmacological Research, 55(3).175–186. DOI: 10.1016/j.phrs.2007.01.010.

D'souza, D., Ranganathan, M. 2015. Medical marijuana: Is the cart before the horse? JAMA. 313(24): 2431–2432. doi: 10.1001/jama.2015.6407.

Delaveau, P., Guillemain, J., Narcisse, G., Rousseau, A. 1989. Neuro-depressive properties of essential oil of lavender. C R Seances Soc Biol Fil. 183(4):342-8.

Dickson, D.W., Feany, M.B., Yen, S.H., Mattiace, L.A., Davies, P. 1996. Cytoskeletal pathology in non-Alzheimer degenerative dementia: new lesions in diffuse Lewy body disease, Pick's disease, and corticobasal degeneration. J Neural Transm Suppl. 47:31-46.

Dietz, B.M., Mahady, G.B., Pauli, G.F., Farnsworth,N.R. 2005. Valerian extract and valerenic acid are partial agonists of the 5-HT5a receptor in vitro. Molecular Brain Research.138(2):191-197.DOI: 10.1016/j.molbrainres.2005.04.009

El-Alfy, A., Ivey, K., Robinson, K., Ahmed, S., Radwan,M., Slade,D., Khan, I., ElSohly, M., Rossb, S. 2010. Antidepressant-like effect of Δ9-tetrahydrocannabinol and other cannabinoids isolated from *Cannabis sativa* L. Pharmacol Biochem Behav. 95(4): 434–442. DOI: 10.1016/j.pbb.2010.03.004.

Elikottil, J., Gupta, P.,Gupta , K. 2009. The Analgesic Potential of Cannabinoids. J Opioid Manag. 5(6): 341–357.

Elizabetsky E, Marschner J and Souza DO. 1995. Effects of linalool on glutamatergic system in the rat cerebral cortex. Neurochem Res 20:461–465.

El-Marasy, S.A., El-Shenawy, S.M., El-Khatib ,A.S., Shabrawy, O.A., Kenawy, S.A. 2012 "Effect of Nigella sativa and wheat germ oils on scopolamine-induced memory impairment in rats" Bull Fac Pharm Cairo Univ. 50.(2) 81-88 .DOI: 10.1016/j.bfopcu.2012.05.001.

Watanabe, E., Kuchta, K.., Kimura, M. 2015. Effects of Bergamot (*Citrus bergamia* (Risso) Wright & Arn.) Essential Oil Aromatherapy on Mood States, Parasympathetic Nervous System Activity, and Salivary Cortisol Levels in 41 Healthy Females.22:43–49. DOI: 10.1159/000380989.

Ezz, H.S., Khadrawy, Y.A., Noor, N.A. 2011. The neuroprotective effect of curcumin and Nigella sativa oil against oxidative stress in the pilocarpine model of epilepsy: a comparison with valproate. Neurochem Res. 36:2195-204. DOI: 10.1007/s11064-011-0544-9.

Fereshteh, G., Shamim,S., Zahra, T., Monir, B. 2016. The Effect of Inhalation of Essential Oils of Polianthes Tuberosa on Test Anxiety in Students: A Clinical Trial. Iran J Med Sci. 41 (3 Suppl).

Ferrara, LA., Raimondi, S.A., D'Episcopo,L., Guida, L., Russo,A.D.,Marotta, T. 2000. Olive oil and reduced need for antihypertensive medications, Archives of Internal Medicine.160 (6).837–842.

Fiebich, B., Heinrich, M., Langosc, J., Kammerer, N., Lieb K. 1999. Antibacterial activity of hyperforin from St John's wort. Lancet. 354: 777.

Filomena, L., Luigino, A., Giancotti, S., Ilari. 2016. Inhibition of Spinal Oxidative Stress by Bergamot Polyphenolic Fraction Attenuates the Development of Morphine Induced Tolerance and Hyperalgesia in Mice" PLoS ONE. 11:5. DOI: doi.org/10.1371/journal.pone.0156039.

Franco, L., Sánchez, C., Bravo, R., Rodriguez, A., Barriga, C., Juánez, J.C.2012. The sedative effects of hops (Humulus lupulus), a component of beer, on the activity/rest rhythm. Acta Physiol Hung.99(2):133-9. DOI: 10.1556/APhysiol.99.2012.2.6.

Fusar-Poli, P., Allen, P., Bhattacharyya, S., Crippa, J., Mechelli, A., Borgwardt, S., Zuardi, A. 2010. Modulation of effective connectivity during emotional processing by Δ9-tetrahydrocannabinol and cannabidiol. International Journal of Neuropsychopharmacology.13(4): 421–432.

Gilhotra, N., Dhingra, D.2011. Thymoquinone produced antianxietylike effects in mice through modulation of GABA and NO levels. Pharmacol Rep. 63(3):660-669.DOI: 10.1016/S1734-1140(11)70577-1.

Goepfert, M., Liebl, P., Herth, N., Ciarlo, G., Buentzel, J., Huebner J. 2017. Aroma oil therapy in palliative care: a pilot study with physiological parameters in conscious as well as unconscious patients. J Cancer Res Clin Oncol. 143(10):2123-2129. DOI: 10.1007/s00432-017-2460-0

Gomes, F., Casarotto, P., Resstel, L., Guimarães, F., 2011. Facilitation of CB1 receptor-mediated neurotransmission decreases marble burying behavior in mice. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 35(2):434–438.

González, S., Sagredo, O., Gómez, M., Ramos, J. 2002 Guía Básica sobre los Cannabinoides. Sociedad Española De Investigación Sobre Cannabinoides. Vol.1, chapter 1. pp. 13.

Gowing, L.R., Ali, R.L., Christie, P., White, J.M. 1998. Therapeutic use of cannabis: clarifying the debate. Drug and Alcohol Review 17: 445-452.

Grant, J., Odlaug, B., Chamberlain, S.,Kim, S. 2011. Dronabinol, a cannabinoid agonist, reduces hair pulling in trichotillomania: A pilot study. Psychopharmacology. 218(3): 493–502.

Greco, R., Gasperi, V., Maccarrone, M., Tassorelli, C. 2010. The endocannabinoid system and migraine. Exp Neurol. 224:85-91.

Greene, R. 1872. Cannabis indica in the treatment of migraine. Practitioner. 41:267-270.

Griffith, T.N., Varela-Nallar ,L., Dinamarca ,M.C., Inestrosa, N.C. 2010. Neurobiological effects of Hyperforin and its potential inAlzheimer's disease therapy. Curr Med Chem. 17: 391–406.

Guha, D., Biswas, D., Purkayastha, S. 2005. Suppression of penicillin-induced epileptiform activity by Nigella sativa: possible mediation by neurotransmitters. Biogenic Amines. 4 (6): 309-321.

Gupta, A., Vij, G., Chopra, K. 2010. Possible role of oxidative stress and immunological activation in mouse model of chronic fatigue syndrome and itsattenuation by olive extract, Journalof Neuroimmunology. 226. (1-2) .3–7. DOI: https://doi.org/10.1016/j.jneuroim.2010.05.021.

Gurley, B.J., Gardner, S.F., Hubbard, M.A., Williams, D.K., Gentry, W.B., Cui, Y., Ang, C.Y. 2005. Clinical assessment of effects of botanical supplementation on cytochrome P450 phenotypes in the elderly: St John's wort, garlic oil, Panax ginseng and Ginkgo biloba. Drugs Aging. 22: 525–539.

Hajiaghaee, R., Faizi, M., Shahmohammadi, Z., Abdollahnejad, F., Naghdibadi ,H., Najafi, F., Razmi ,A. 2016. Hydroalcoholic extract of Myrtus communis can alter anxiety and sleep parameters: a behavioural and EEG sleep pattern study in mice and rats. Pharm Biol. 54(10):2141-8. DOI: 10.3109/13880209.2016.1148175

Hampson, A.J., Grimaldi, M., Lolic, M., Wink, D., Rosenthal, R., Axelrod, J. 2000. Neuroprotective antioxidants from marijuana. Ann N Y Acad Sci. 899:274-282.

Hepler, R.S., Frank, I.R. 1971. Marihuana smoking and intraocular pressure. JAMA. 217:1392.

Hobbs, C. 1989. Valerian: a literature review. HerbalGram. 21:19-34.

Holzl, J., Godau, P. 1989. Receptor binding studies with Valeriana officinalis on the benzodiazepine receptor. Planta medica. 55: 642

Hosseini, M., Zakeri, S., Khoshdast, S., Yousefian, F.T., Rastegar, M., Vafaee, F., Kahdouee, S., Ghorbani, F., Rakhshandeh, H., Kazemi, S.A. 2012. The effects of Nigella sativa hydro-alcoholic extract and thymoquinone on lipopolysaccharide - induced depression like behavior in rats. J Pharm Bioallied Sci. 4(3):219-2. DOI: 10.4103/0975-7406.99052.

Howlett, A.C. 2004. Efficacy in CB1 receptor-mediated signal transduction. Br J Pharmacol. 142:1209-1218.

Imai, H., Kotegawa, T., Tsutsumi, K., Takuya, M., Nobuoki, E., Shigeyuki, N., Kyoichi, O. 2008. The recovery timecourseof CYP3A after induction by St John's wort administration. Br J Clin Pharmacol. 65: 701–707. DOI: 10.1111/j.1365-2125.2008.03120.x.

Ismail, N., Ismail, M., Mazlan, M., Latiff, L.A., Imam, M.U., Iqbal, S., Azmi, N.H., Ghafar, S.A., Chan, K.W. 2013. Thymoquinone prevents beta-amyloid neurotoxicity in primary cultured cerebellar granule neurons. Cell Mol Neurobiol. 33(8):1159–1169

Janardhanan, A., Sadanand, A., Vanisree, A.J. 2016. Nardostachys jatamansi Targets BDNF-TrkB to Alleviate Ketamine-Induced Schizophrenia-Like Symptoms in Rats. Neuropsychobiology. 74(2):104-114. DOI: 10.1159/000454985.

Jones, N.A., Hill, A.J., Smith, I., Bevan, S.A., Williams, C.M., Whalley, B.J.,Stephens ,G.J. 2010. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. J Pharmacol Exp Ther. 332(2):569–77. DOI: 10.1124/jpet.109.159145.

Kamm-Kohl, A.V., Jansen, W., Brockmann, P .1984. Moderne Baldriantherapie gegen nervose storungen im senium. Medwelt. 35:1450–1454.

Kaltschmidt, B., Heinrich, M., Kaltschmidt, C. 2002. Stimulus-dependent activation of NF-kappaB specifies apoptosis or neuroprotection in cerebellar granule cells. Neuromol. Med. 2: 299–309.

Kantarcioglu, A., Kiraz N., Aydin A. 2015. Microbiota-Gut-Brain axis: yeast Species isolate from Stool Samples of Children with Suspected or Diagnosed Autism Spectrum Disorders and In vitro Susceptibility against Nystatin and Fluconazole. Mycopathology 181(1-2):1-7.

Kanter, M. 2008. Nigella sativa and derived thymoquinone prevents hippocampal neurodegeneration after chronic toluene exposure in rats. Neurochem Res. 33:579-88. DOI: 10.1007/s11064-007-9481-z

Kasper, S., Caraci, F., Forti, B., Drago, F., Aguglia, E. 2010. Efficacy and tolerability of Hypericum extract for the treatment of mild to moderate depression. EurNeuropsychopharmacol. 20: 747–765.

Kasper, S., Volz, H.P., Moller, H.J., Dienel, A., Kieser, M. 2008. Continuation and long-term maintenance treatment with Hypericumextract WS 5570 after recovery from an acute episode of moderate

depression a double-blind, randomized, placebo controlled long-term trial. EurNeuropsychopharmacol .18: 803–813.

Kaspera, S., Gastparb, M., Müllerc, W., Volzd, H., Mö llere, H., Dienelf, A., Schlä fkef, A. 2010. Silexan, an orally administered Lavandula oil preparation, is effective in the treatment of 'subsyndromal' anxiety disorder: a randomized, double-blind, placebo controlled trial. Int Clin Psychopharmacol. 25:277–287.

Kennedy, D. O., Pace, S., Haskell, C., Okello, E. J., Milne, A., Scholey, A. B. 2006. Effects of cholinesterase inhibiting sage (salvia officinalis) on mood, anxiety and performance on a psychological stress or battery. Neuropsychopharmacology. 31(4): 845-52. DOI: 10.1038/sj.npp.1300907.

Keys, A., Menotti, A., Karvonen, M.J.1986.The diet and 15-year death rate in the seven countries study,"American Journal of Epidemiology. 124(6): 903–915.

Khan, I., Karim, N., Ahmad, W., Abdelhalim, A., Chebib, M. 2016. GABA-A Receptor Modulation and Anticonvulsant, Anxiolytic, and Antidepressant Activities of Constituents from Artemisia indica Linn. Evid Based Complement Alternat Med.1215393. DOI: 10.1155/2016/1215393.

Khan, R.A., Riaz, A. 2015. Behavioral effects of Citrus limon in rats. Metab Brain Dis.30: 589-596. DOI: 10.1007/s11011-014-9616-2.

Kimball, E.S., Wallace, N.H., Schneider, C.R., D'Andrea, M.R., Hornby, P.J. 2010. Small intestinal cannabinoid receptor changes following a single colonic insult with oil of mustard in mice. Front Pharmacol. 1:1-8.

Kostomoiri, M., Fragkouli, A., Sagnou M., Skaltsounis, L.A., Pelecanou, M., Tsilibary, E.C., Szinia, A.K. 2013. Oleuropein, an antioxidant polyphenol constituent of olive promotes α-secretase cleavage of the amyloid precursor protein (AβPP). Cell Mol Neurobiol.33:147–154.

Kourosh, S., Mahmoud, B., Mahmoud, R., Hassan, H., Kamran, D., Fariba, B., Jafar, A. 2014. The most common native medicinal plants used for psychiatric and neurological disorders in Urmia city, northwest of Iran. Asian Pac J Trop Dis. 4(2): S895-S901.DOI: 10.1016/S2222-1808(14)60754-4.

Kozics, K., Srancikova, A., Sedlackova, E., Horvathova, E., Melusova, M., Melus, V., Krajcovicova, Z., Sramkova M. 2017. Antioxidant potential of essential oil from Lavandula angustifolia in in vitro and ex vivo cultured liver cells. Neoplasma. 64(4):485-493. DOI: 10.4149/neo_2017_401.

Kuddus, M., Ginawi, I.A.M., Al-Hazimi, A. 2013. Cannabis sativa: An ancient wild edible plant of India. Emir J Food Agric. 25:736-745.

Laakmann, G., Schule, C., Baghai, T., Kieser, M. 1998. St John's wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy. Pharmacopsychiatry .31: 54-59.

Lacher, S. K., Mayer, R., Sichardt, K. 2007. Interaction of valerian extracts of different polarity with adenosine receptors: Identification of isovaltrate as an inverse agonist at A1 receptors.73(2):248-258. DOI: 10.1016/j.bcp.2006.09.029

Leatherwood, P., Chauffard, F., Heck, E., Munoz-Box, E. 1982. Aqueous extract of valerian root (Valeriana officinalis L.) improves sleep quality in man. Pharmacol Biochem Behav.17(1):65-71.DOI: 10.1016/0091-3057(82)90264-7.

Lehrner, J., Marwinski ,G., Lehr ,S., Johren, P., Deecke, L.2005. Ambient odors of orange and lavender reduce anxiety and improve mood in a dental office. Physiol Behav. 15: 86(1-2):92-5. DOI:10.1016/j.physbeh.2005.06.031

Leri, M., Nosi, D., Natalello, A, et al. 2016. The polyphenol Oleuropein aglycone hinders the growth of toxic transthyretin amyloid assemblies. J Nutr Biochem. 30:153–166. DOI: 10.1016/j.jnutbio.2015.12.009.

Leuschner, J., Muller, J., Rudmann, M. 1993. Characterization of the central nervous depressant activity of a commercially available valerian root extract. Arzneimittelforschung. 43(6):638-641

Lim, D.W., Lee, M.S., Her, S., Cho, S., Lee, C.H., Kim, I.H., Han, D. 2016. Antidepressant-Like Effects of Lindera obtusiloba Extracts on the Immobility Behavior of Rats in the Forced Swim Test. Molecules. 21(3): 277. DOI: 10.3390/molecules21030277.

Lindahl, O., Lindwell, L. 1989. Double-blind study of a valerian preparation. Pharmacol Biochem Behav.32(4):1065-1066

Linde, K. 2009. St. John's wort - an overview. Forsch. Komplementmed. 16:146–155.

Logan, A.C. 2003. Neurobehavioral aspects of omega-3 fatty acids: possible mechanisms and therapeutic value in major depression. Alternative Medicine Review. 8.(4):410–425.

López, V., Nielsen, B., Solas, M., Ramírez, M.J., Jäger, A.K. 2017. Exploring Pharmacological Mechanisms of Lavender (*Lavandula angustifolia*) Essential Oil on Central Nervous System Targets. Front.

Pharmacol. 8:280. DOI: 10.3389/fphar.2017.00280.

Luo, L., Sun, Q., Mao, Y., Lu, Y., Tan, R. 2004. Inhibitory effects of flavonoids from Hypericumperforatumon nitric oxide synthase. J. Ethnopharmacol. 93,221-225.

Machowetz, A., Poulsen, H.E., Gruendel, S. et al., 2007. Effect of olive oils on biomarkers of oxidative DNA stress in Northern and Southern Europeans, FASEB Journal. 21. (1): 45–52.

Mahendra, P., Bisht, S. 2011.Anti-anxiety activity of Coriandrum sativum assessed using different experimental anxiety models. Indian J Pharmacol. 3(5):574-7

Mallick, N., Khan, R.A. 2016. Behavioral effects of Citrus paradisi in rats. Metab Brain Dis. (2): 329-35. DOI: 10.1007/s11011-015-9754-1

Mark, M., Lorraine, O.2012. Plasma 1, 8-cineole correlates with cognitive performance following exposure to rosemary essential oil aroma. Ther Adv Psychopharmacol. 2(3): 103–113.DOI: 10.1177/2045125312436573

Marzouk, T., El-Nemer, A., Baraka, H. 2013. The effect of aromatherapy abdominal massage on alleviating menstrual pain in nursing students: A Prospective Randomized Cross-Over Study. Evidence-Based Complementary and Alternative Medicine. Evidence-Based Complementary and Alternative Medicine. 74242. DOI: 10.1155/2013/742421

Mayer, E.A., Tillisch, K., Gupta, A. 2015. Gut/brain axis and the microbiota. The Journal of Clinical Investigation, 125(3): 926–938. DOI: 10.1172/JCI76304

McGeeney, B.E. 2013. Cannabinoids and hallucinogens for headache. Headache. 53:447-458

McGimpsey, J.A., Porter, N.G. 1999. Lavender, A grower´s guide for commercial production. New Zeland institute for Crop & Food Research Ltd., New Zeland. 2:62

Mechan, A.O., Fowler, A., Seifert, N., Rieger, H., Wöhrle, T., Etheve, S., Wyss, A., Schüler, G., Colletto, B., Kilpert, C., Aston, J., Elliott, J.M., Goralczyk, R., Mohajeri, M.H. 2011. Monoamine reuptake inhibition and mood-enhancing potential of a specified oregano extract. Br J Nutr.105(8): 1150-63. DOI: 10.1017/S0007114510004940.

Mei, L., Mochizuki, M., Hasegawa, N. 2014. Pycnogenol ameliorates depression-like behavior in repeated corticosterone-induced depression mice model. Biomed Res Int. 942927. DOI: 10.1155/2014/942927

Melliou, E., Michaelakis, A., Koliopoulos, G., Skaltsounis, A.L., Magiatis, P. 2009. High quality bergamot oil from Greece: Chemical analysis using chiral gas chromatography and larvicidal activity against the West Nile virus vector. Molecules.14: 839–849.

Mennini, T., Bernasconi, P., et al. 1993. In vitro study in the interaction of extracts and pure compounds from Valerian officinalis roots with GABA, benzodiazepine and barbiturate receptors. Fitoterapia. 64: 291– 30

Mesfin, M., Asres, K., Shibeshi, W. 2014. Evaluation of anxiolytic activity of the essential oil of the aerial part of Foeniculum vulgare Miller in mice. BMC Complement Altern Med. 14:310. DOI: 10.1186/1472-6882-14-310

Min,Seo., Sowndhararajan, S., Songmun, K.2016. Influence of Binasal and Uninasal Inhalations of Essential Oil of Abies koreana Twigs on Electroencephalographic Activity of Human.Behavioural Neurology.Article. 9250935. DOI:10.1155/2016/9250935

Mohamed, A., Waris, H.M., Ramadan, H., Quereshi, M., Kalra, J. 2009. Amelioration of chronic relapsing experimental autoimmune encephalomyelitis (cr-eae) using thymoquinone. Biomed Sci Instrum. 45:274-279

Moon, S., Lee, M.S., Jung, S., Kang, B., Kim, S.Y., Park, S., Son, H.Y., Kim,C.T., Jo, Y.H., Kim,I.H, Kim,Y.S., Kim, Y.2017. High Hydrostatic Pressure Extract of Ginger Exerts Antistress Effects in Immobilization-Stressed Rats. J Med Food. 20(9): 864-872. DOI: 10.1089/jmf.2017.3955

Moraes, A., Almeida, L., Costa, M. 2006. Effects of the essential oil from Citrus aurantium L. in experimental anxiety models in mice. Life Sci. 78(15):1720-5. DOI:10.1016/j.lfs.2005.08.004.

Morris, N. 2002. The effects of lavender (Lavendula angustifolium) baths on psychological well-being: two exploratory randomized controls trials. Complementary Therapies in Medicine.10 (4) :223–228.

Motallebnejad, M., Moghadamnia, A., Talei, M. 2008. The efficacy of Hypericumperforatum extract on recurrent aphthous ulcers. J. Med. Sci. 8:39–43.

Moussaieff, A., Gross, M., Nesher, E., Tikhonov, T., Yadid, G., Pinhasov, A. 2012. Incensole acetate reduces depressive-like behavior and modulates hippocampal BDNF and CRF expression of submissive animals. J Psychopharmacol. 26(12): 1584-93. DOI: 10.1177/0269881112458729

Movafegh, A., Alizadeh, R., Hajimohamadi, F., Esfehani, F., Nejatfar, M. 2008. Preoperative oral Passiflora incarnata reduces anxiety in ambulatory surgery patients: a double-blind, placebo-controlled study. Anesth Analg.Jun.

106(6):1728-32. DOI: 10.1213/ane.0b013e318172c3f9.

Muller, W., Rolli, M., Schafer, C., Hafner, U. 1997. Effects of hypericum extract (LI 160) in biochemical models of antidepressant activity. Pharmacopsychiatry.30: 102-107

Muller-Vahl, K.R., Kolbe, H., Schneider, U., Emrich, H.M. 1999. Cannabis in movement disorders. Forsch Komplementarmed. 6(3):23-27.

Naftali, T., Bar-Lev, L., Dotan, I., Lansky, E.P., Sklerovsky, F., Konikoff, F.M. 2013. Cannabis induces a clinical response in patients with Crohn's disease: A prospective placebo-controlled study. Clin Gastroenterol Hepatol. 11:1280-e1.

Nangia, M., Syed, W., Doraiswamy, P.M. 2000. Efficacy and safety of St. John's wort for the treatment of major depression. Public Health Nutr 3: 487–494.

Okmen, G., Neslihan, B. 2017. The Biological Activities of HypericumperforatumL. Afr J Tradit Complement Altern Med.14 (1): 213-218.

Oliveira, A.I., Pinho, C., Sarmento, B., Dias, A.C.P. 2016. Neuroprotective Activity of Hypericumperforatum and Its Major Components. Front. Plant Sci. 7:1004.

Osler, W., McCrae, T. 1915. The Principles and Practice of Medicine. New York: Appleton; 1915.

Pacher, P., Bátkai, S., Kunos, G. 2006. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacological Reviews. 58(3): 389–462.

Patocka, J. 2003. The chemistry, pharmacology, and toxicology of the biologically active constituents of the herb Hypericumperforatum L. J. Appl. Biomed. 1: 61–70.

Patočka, J., Jakl, J. 2010. Biomedically relevant chemical constituents of Valeriana officinalis. Journal of applied biomedicine. 8(1):11-18.DOI: 10.2478/v10136-009-0002-z

Hossein Koulivand, P., Khaleghi Ghadiri, M., Gorji, A. 2013. Lavender and the Nervous System Evidence-Based Complementary and Alternative Medicine. Evid Based Complement Alternat Med. 681304. DOI: 10.1155/2013/681304

Perloff, M.D., von Moltke, L.L., Störmer, E., Shader, R.I., Greenblatt, D.J. 2001. Saint John's wort: an in vitro analysis of P-glycoprotein induction due to extended exposure. Br J Pharmacol. 134: 1601–1608.

Perveen, T., Haider, S., Kanwal, S., Haleem, D.J. 2009. Repeated administration of Nigella sativa decreases 5-HTturnover and produces anxiolytic effects in rats. Pak J Pharm Sci. 2282:139-144

Petersen, R. 1976. Marihuana research findings. Summary. NIDA Res Monogr. 14:1–37. U.S. Department of health, education, and welfare, Public Health Service

Pinar-Sueiroa, S., Rodríguez-Puertasb, R., Vecino, E. 2011. Aplicaciones de los cannabinoides en glaucoma. Arch Soc Esp Oftalmol. 86(1):16-23

Pitt, J., Roth, W., Lacor, P., et al. 2009. Alzheimer's-associated Aβ oligomers show altered structure, immunoreactivity and synaptotoxicity with low doses of oleocanthal. Toxicol Appl Pharmacol. 240:189– 197.

Porter, B.E., Jacobson, C. 2013. Report of a parent survey of cannabidiolenriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy Behav. 29(3):574–7.

Potter, D.J. 2014. A review of the cultivation and processing of cannabis (Cannabis sativa L.) for production of prescription medicines in the UK. Drug Testing and Analysis. 6: 31–38.

Press, C.A, Knupp, K.G and Chapman, K.E.2015. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. Epilepsy Behav. 45:49–52.

Radad, K., Moldzio, R., Taha, M., Rausch, W.D. 2009. Thymoquinone protects dopaminergic neurons against MPP+ and rotenone. Phytother Res. 23(5): 696-700. DOI: 10.1002/ptr.2708

Rahimi, R., Nikfar, S., Abdollahi, M. 2009. Efficacy and tolerability of Hypericumperforatum in major depressive disorder incomparison with selective serotonin reuptake inhibitors: a meta-analysis. ProgrNeuropsychopharmacolBiol Psychiatry.33 : 118–127.

Rahimikian, F., Rahimi, R., Golzareh, P., Bekhradi, R., Mehran, A. 2017. Effect of Foeniculum vulgare Mill. (fennel) on menopausal symptoms in postmenopausal women: a randomized, triple-blind, placebo-controlled trial. Menopause. 24(9):1017-1021. DOI: 10.1097/GME.0000000000000881.

Rigacci, S., Guidotti, V., Bucciantini, M, et al. 2010. Oleuropein aglycon prevents cytotoxic amyloid aggregation of human amylin. J Nutr Biochem. 21:726–735

Rigacci, S., Guidotti, V., Bucciantini, M., Nichino, D., Relini, A., Berti, A., Stefani, M. 2011. Aβ (1-42) aggregates into non-toxic amyloid assemblies in the presence of the natural polyphenol oleuropein aglycon. Curr Alz Res. 8:841-52.

Rock, E., Bolognini, D., Limebeer, C., Cascio, M., Anavi-Goffer, S., Fletcher, P., Parker L. 2012. Cannabidiol, a non-psychotropic component of cannabis, attenuates vomiting and nausea-like behavior via indirect agonism of 5-HT1A somatodendritic autoreceptors in the dorsal raphe nucleus. British Journal of Pharmacology, 165(8):2620– 2634.

Rodríguez, F., Del Arco, I., Bermúdez-Silva, F.J., Bilbao, A., Cippitelli, A., Navarro, M. 2005. The endocannabinoid system: Physiology and pharmacology. Alcohol Alcohol. 40:2-14.

Rodriguez, R. 2012. Los productos de Cannabis sativa: situación actual y perspectivas en medicina. Salud Ment. 35 (3).247-256.

Rombolà, L., Tridico, L., Scuteri, D., Sakurada, T., Shinobu, S., Mizoguchi, H., Avato, P., Corasaniti, M.T., Bagetta, G., Morrone, L.A. 2017. Bergamot Essential Oil Attenuates Anxiety-Like Behaviour in Rats;Molecules. 11(22). DOI: 10.3390/molecules22040614

Romero,C., Medina, E., Vargas, J.,Brenes,M., De Castro,A .2007. In vitro activity of olive oil polyphenols against helicobacter pylori. JournalofAgriculturalandFoodChemistry. 55(3):680–686.

Russo, E., Scicchitano, F., Whalley, B.J., Mazzitello, C., Ciriaco, M., Esposito, S., Patanè, M., Upton, R., Pugliese, M., Chimirri, S., Mammì, M., Palleria, C., De Sarro, G. 2014. Hypericumperforatum: pharmacokinetic, mechanism of action, tolerability, and clinical drug-drug interactions. Phytother Res. 28(5):643-55. DOI: 10.1002/ptr.5050.

Saddiqe, Z., Naeem, I., Maimoona, A. 2010. A review of the antibacterial activity of HypericumperforatumL. J Ethnopharmacol. 131: 511–521.

Saeki, S., Mayumi, S. 2001. Physiological effects of inhaling fragrances. Int. J. Aromather. 11: 118-25.

Saiyudthong, S., Pongmayteegul, S., Marsden, C., Phansuwan-Pujito, P.2015. Anxiety-like behaviour and c-fos expression in rats that inhaled vetiver essential oil. Natural Product Research. 29 (22): 2141-2144. DOI: 10.1080/14786419.2014.992342.

Sakamoto, T., Mitani, Y., Nakajima, K. 1992. Psychotropic effects of Japanese valerian root extract. Chem Pharm Bull.40 (3):758-761

Sandler, R., Finegold, S., Bolte, E., Buchanan, C., Maxwell, M., Vaisanen, M., Nelson, M., Wexler, H. 2000. Short-term Benefit from Oral Vancomycin Treatment of Regressive-Onset Autism. Journal of Child Neurology. 15:429.

Sayyah, M., Sayyah, M., Kamalinejad, M. 2006. A preliminary randomized double blind clinical trial on the efficacy of aqueous extract of Echium amoenum in the treatment of mild to moderate major depression. Prog Neuropsychopharmacol Biol Psychiatry.30(1):166-9. DOI: 10.1016/j.pnpbp.2005.10.005.

Schempp, C., Pelz, K., Wittmer, A., Schopf, E., Simon, J. C. 1999. Antibacterial activity of hyperforin from St John's wort, against multiresistantStaphylococcus aureus and gram-positive bacteria. Lancet. 353: 2129.

Schindler, F., Anghelescu, I., Regen, F., Jockers-Scherubl, M. 2008. Improvement in refractory obsessive-compulsive disorder with dronabinol. American Journal of Psychiatry. 165(4): 536–537.

Schrader, E. 2000. Equivalence of St John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study mild-moderate depression. Int. J. Clin. Psychopharmacol. 15: 61-68.

Schulz, V., Hansel, R., Tyler, V.E. 1997. Rational phytotherapy: a physician's guide to herbal medicine. Berlin: Springer 306.Germany.

Selkoe, D.J. 2003. Folding proteins in fatal ways. Nature.426:900– 904.

Serrano, A., Parsons, L.H. 2011. Endocannabinoid influence in drug reinforcement, dependence and addiction-related behaviors. Pharmacol Ther. 132:215-241.

Sharrif, M. 2011. Nigella sativa Traditional Usages (BlackSeed) Adv Environ Biol.5(1):5–16

Si, W., Chen., Li Min., Wei Jing Li., Wei XiKong., Jing FangLi, et al. 2004. The effects of angelica essential oil in three murine tests of anxiety. Pharmacology Biochemistry and Behavior. 79(2):377-382. DOI: 10.1016/j.pbb.2004.08.017

Silva, B., Oliveira, P., Dias, A., Malva, J. 2008. Quercetin, kaempferol and biapigenin from Hypericumperforatum are neuroprotective against excitotoxic insults. Neurotox. Res. 13: 265–279.

Silva, G.L., Luft, C., Lunardelli, A., Amaral, R.H., Melo, D.A., Donadio, M.V., Nunes, F.B., De Azambuja, M.S., Santana, J.C., Moraes, C.M., Mello, R.O., Cassel, E., Pereira, M.A., De Oliveira, J.R. 2015. Antioxidant, analgesic and anti-inflammatory effects of lavender essential oil. An Acad Bras Cienc. 87(2):1397-408. DOI: 10.1590/0001-3765201520150056.

Singer, A., Wonnemann, M., Muller,W. E. 1999. Hyperforin, a major antidepressant constituent of St. John's wort, inhibits serotonin uptake by elevating free

intracellular Na+. J. Pharmacol. Exp. Ther. 290: 1363-1368.

Singer, A., Wonnemann, M., Muller, W. E. 2000. Hyperforin alters free intracellular H+ and Na+ concentration in human platelets [abstract]. Proceedings of the Biocenter Symposium on Drug Therapy. Pharmacology of St. John's wort (Hypericumperforatum L.) and its constituents. University of Frankfurt, Germany.

Sirtori, C.R., Anderson, J.W., Arnoldi, A. 2007. Nutritionaland nutraceutical considerations for dyslipidemia, Future Lipidology.2 (3)313–339.

Solfrizzi, V., Panza, F., Torres, F., et al. 2003. High monounsaturated fatty acids intake protects again stage-related cognitive decline. Neurology.52 (8):1563–1569, 1999.

Spillantini, M.G., Schmidt, M.L., Lee, V.M.Y., Trojanowski, J.Q., Jakes, R., Goedert, M. 1997. α-Synuclein in Lewy bodies. Nature. 388(6645):839-40.

Staffeldt, B., Kerb, R., Brockmöller, J., Ploch, M., Roots, I. 1994. Pharmacokinetics of hypericin and pseudohypericin after oralintake of the Hypericumperforatum extract LI 160 in healthy volunteers. J Geriatr Psychiatry Neurol. 7: 47–53.

Suntar, I., Akkol E., Yilmazer, D., Baykal, T., Kirmizibekmez, H., Alper M., et al. 2010. Investigations on the in vivo wound healing potential of Hypericumperforatum L. J. Ethnopharmacol. 127:468–477.

Suzuki, O., Katsumata, Y., Oya, M., Bladt, S., Wagner, H. 1984. Inhibition of monoamine oxidase by hypericin. Planta Med. 50: 272-274.

Tadaaki, S., Michiyo, M., Haruna, S., Hideo, Y. 2013. Prolonged anxiolytic-like activity of sandalwood (Santalum album L.) oil in stress-loaded mice. 29 (1):35. DOI: 10.1002/ffj.3176

Perveen, T., Hashmi, B.M., Haider, S., Tabassum, S., Saleem, S., Siddiqui, M.A. 2013. Role of Monoaminergic System in the Etiology of Olive Oil Induced Antidepressant and Anxiolytic Effects in Rat. ISRN Pharmacol. 10:615-685. DOI: 10.1155/2013/615685.

Takeuchi, H., Kondo, Y., Yanagi, M., Yoshikawa, M. 2000. Accelerative effect of olive oil on adrenal corticosterone secretion in rats loaded with single or repetitive immersion-restraint stress, Journal of Nutritional.46 (4):158-161. DOI: 10.3177/jnsv.46.158.

Tampi, R.R., Tampi, D.J. 2014. Efficacy and Tolerability of Benzodiazepines for the Treatment of Behavioral and Psychological Symptoms of Dementia: A Systematic Review of Randomized Controlled Trials. Am. J. Alzheimer Dis. Other Dement. 29: 565–574.

Taponen, S., Simojoki, H., Haveri, M., Larsen, H., Pyorala, S. 2006. Clinical characteristics and persistence of bovine mastitis caused by different species of coagulase-negative Staphylococci identified with API or AFLP. Vet. Microbiol. 115:199–207.

Thiebaut, F., Tsuruo, T., Hamada, H., Gottesman, M.M., Pastan, I., Willingham, M.C. 1987. Cellular localization of the multidrugresistancegene product P-glycoprotein in normal humantissues. Proc Natl AcadSci. 84: 7735–7738.

Thiede, H., Walper, A. 1994. Inhibition of MAO and COMT by Hypericum extracts and hypericin. J. Ger. Psychiatry Neurol. 7: 54-56.

Thomas, A., Baillie, G., Phillips, A., Razdan, R., Ross, R., Pertwee, R. 2007. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. British Journal of Pharmacology.150(5):613–623.

Tian, J. 2014. Antidepressant-like activity of adhyperforin, a novel constituent of Hypericumperforatum L. Sci. Rep. 4: 5632.

Togna, G.I., Togna, A.R., Franconi, M., Marra, C., Guiso, M. 2003.Olive oil isochromans inhibit human platelet reactivity. JournalofNutrition.133 (8): 2532–2536.

Ullah, I., Ullah, N., Naseer, M.I., Lee, H.Y., Kim, M.O. 2012. Neuroprotection with metformin and thymoquinone against ethanol-induced apoptotic neurodegeneration in prenatal rat cortical neurons. BMC Neurosci. 13:11. DOI: 10.1186/1471-2202-13-11.

Upadhyay, G., Khoshla, S., Kosuru, R., Singh, S. 2016. Anxiolytic, antidepressant, and antistress activities of the aqueous extract of Cinnamomum tamala Nees and Eberm in rats. Indian J Pharmacol. 48(5):555-561

Upton, R. 1997. St. John's wort (Hypericumperforatum). American Herbal Pharmacopoeia (AHP). In HerbalGram 40. American Herbal Pharmacopoeia: Santa Cruz. 132.

Vanhaelen, M., Vanhaelen-Fastre, R. 1983. Quantitative determination of biologically active constituents in medicinal plant crudeextracts by thin-layer chromatography-densitometry. J. Chromatogr.281: 263-271.

Veith, J., Schneider, G., Lemmer, B., Willems, M. 1986. The effect of degradation products of valepotriates on the motor activity of light-dark synchronized mice. Planta Med. 179-83

Verotta, L., Appendino, G., Jakupovic, J., Bombardelli, E. 2000. Hyperforin analogues from St John's wort (Hypericumperforatum). J. Nat. Prod. 63: 412-415.

Wallace, M.J., Martin, B.R., DeLorenzo, R.J. 2002. Evidence for a physiological role of endocannabinoids in themodulation of seizure threshold and severity. Eur J Pharmacol. 452(3):295–301.

Whiting, P.F., Wolff, R.F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A.V., Keurentjes, J.C., Lang, S., Misso, K., Ryder, S., Schmidlkofer, S., Westwood,M., Kleijnen, J. 2015. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 313(24):2456-73. DOI: 10.1001/jama.2015.6358.

Woelk, H., Arnoldt, K.H., Kieser, M., Hoerr, R. 2007. Ginkgo biloba special extract EGb 761 in generalized anxiety disorder and adjustment disorder with anxious mood: a randomized, double-blind, placebo-controlled trial. J Psychiatr Res. 41(6):472-80. DOI:10.1016/j.jpsychires.2006.05.004.

Woelk, H., Burkard, G., Grunwald, J. 1994. Benefits and risks of the Hypericum extract LI 160: drug-monitoring study with 3250patients. J Geriatr Psychiatry Neurol. 7: 34–38.

Wolfson, P., Hoffmann, D.L. 2003. An investigation into the efficacy of Scutellaria lateriflora in healthy volunteers. Altern Ther Health Med. 9(2):74-8.

Wonnemann, M., Singer, A., Muller, W.E. 2000. Inhibition of synaptosomal uptake of 3H-L-glutamate and 3H-GABA by hyperforin, a major constituent of St John's wort: the role of amiloride sensitive sodium conductive pathways. Neuropsychopharmacology. 23: 188-197.

World Health Organization. 2010. Medicinal plants commonly used in the Newly Independent States (NIS). Geneve. ISBN 978 92 4 159772 2.

Wu, K., Hanna, G., Rosenberg., Arnold, P. 2012. The role of glutamate signaling in the pathogenesis and treatment of obsessive–compulsive disorder. Pharmacology Biochemistry and Behavior. 100(4): 726–735.

Xie, R., Tan, L.H., Polasek, E.C. et al. 2005. CYP3A and P-glycoproteinactivity induction with St. John’s wort in healthy volunteersfrom 6 ethnic populations. J ClinPharmacol. 45: 352–356.

Yamada, K., Mimaki, Y., Sashida, Y. 2005. Effects of inhaling the vapor of Lavandula burnatii super-derived essential oil and linalool on plasma adrenocorticotropic hormone (ACTH), catecholamine and gonadotropin levels in experimental menopausal female rats. Biological and Pharmaceutical Bulletin.28: 378–379.

Kong, Y., Wang, T., Wang, R., Ma, Y., Song, S., Liu, J., Hu, W., Li, S. 2017. Inhalation of Roman Chamomile Essential Oil Attenuates Depressive-Like Behaviors in Wistar Kyoto Rats. Sci China Life Sci 60 (6): 647-655. DOI:10.1007/s11427-016-9034-8

Yip, Y., Tse, S. 2004. The effectiveness of relaxation acupoint stimulation and acupressure with aromatic lavender essential oil for non-specific low back pain in Hong Kong: a randomized controlled trial. Complementary Therapies in Medicine. 12(1): 28–37.

Yip, Y.B., Tse, S. 2006. An experimental study on the effectiveness of acupressure with aromatic lavender essential oil for sub-acute, non-specific neck pain in Hong Kong. ComplementaryTherapies in Clinical Practice. 12(1): 18–26.

Yu, P.H. 2000. Effect of the Hypericumperforatum extract on serotonin turnover in the mouse brain. Pharmacopsychiatry. 33: 60-65

Zhan, N., Zhang, L., Linyin F. 2016. The anxiolytic effect of essential oil of Cananga odorataexposure on mice and determination of its major active constituents.Phitomedicine. 14:1727-1734. DOI: 10.1016/j.phymed.2016.10.017.

Zhang, X., Du, Q., Liu, C., Yang, Y., Wang, J., Duan, S., Duan, J. 2016. Rhodioloside ameliorates depressive behavior via up-regulation of monoaminergic system activity and anti-inflammatory effect in olfactory bulbectomized rats. Int Immunopharmacol. 36:300-304

**Table 1**. Annex; a summary of studies based in other plants essential oils.

| Essential oil | Participants (diagnosis, *n*) | Results | References |
|---|---|---|---|
| Jasmine *(Jasminum multiflorum)* | Murine Model | Significant anxiolytic effect at a dose that does not affect motor co-ordination. | Addae et al. (2017) |
| Feverfew *(Tanacetum parthenium)* | Murine Model | Anxiolytic- and antidepressant-like effects. | Cárdenas et al. (2017) |
| Frankincense or Incense (species of *Boswellia)* | Murine Model | Reduces depressive-like behavior and modulates hippocampal BDNF and CRF expression of submissive animals | Moussaieff et al. (2012) |
| Borage (*Echium amoenum*) | Depression 35= Mild to moderate major depressive disorder. | In week 4, the extract showed a significant superiority over placebo in reducing depressive symptoms. | Sayyah and Kamalinejad (2006) |
| Roseroot (*Rhodiola rosea*) | Hyperactivity Depression (murine model) | These results confirmed the antidepressant-like effect of rhodioloside, which might be primarily based on its up-regulation of the monoaminergic system activity. | Zhang et al. (2016) |
| Ginkgo (*Ginkgo biloba*) | Anxiety<br>107= anxiety disorder and anxious mood. | Hamilton rating scale for anxiety total scores decreased after the treatment. | Woelk et al. (2007) |
| Blue skullcap *(Scutellaria lateriflora)* | Healthy | Attenuated anxiety and tension on a numerical rating scale. | Wolfson and Hoffmann (2003) |
| Ginger *(Zingiber officinale)* | Murine Model | Anti-stress. | Moon et al. (2017) |
| Passionflower *(Passiflora incarnata)* | Surgery patients | Significant reduction of anxiety in favor of the herb on a numerical rating scale. | Movafegh et al. (2008) |
| Lemon *(Citrus medica limonum)* | Palliative patients 10= control group | Increase in respiration rate, heart rate and diastolic blood pressure in all groups. | Goepfert et al. (2017) |
| Lemon *(Citrus limon)* | 15= conscious Patients<br>5= unconscious Murine model | Anxiolytic activitity. | Khan and Riaz (2015) |
| Hops *(Humulus lupulus)* | 15= animal models (*coturnix coturnix*) | The concentration of 2 mg of hop extract effectively decreased nocturnal activity in the circadian activity rhythm. | Franco et al. (2012) |
| Rosemary (*Rosmarinus officinalis)* | Healthy Patients | Objective effects on cognitive performance, as well as subjective effects on mood. | Mark Moss et al. (2009) |
| Oregano *(Origanum vulgare)* | Murine model | Is a brain-active, with moderate triple reuptake inhibitory activity, and exhibits positive behavioural effects in animal models. | Mechan et al. (2011) |
| Myrtle *(Myrtus communis)* | Murine Model | The anxiolytic, myorelaxant and hypnotic effects. | Hajiaghaee et al. (2016) |
| Spikenard *(Nardostachys jatamansi)* | Murine Model | Anti- schizophrenic. | Janardhanan et al. (2016) |
| Grapefruit *(Citrus paradise)* | Murine model | Anxiolytic and antidepressant activitity. | Mallick and Khan (2016) |
| Pinus *(Pinus pinaster)* | Murine model | Ameliorates depression-like behavior. | Mei et al. (2014) |
| Orange (*Citrus sinensis)* | Patients waiting for dental treatment. | Helpful in reducing anxiety. | Lehrner et al. (2005) |

**Table 1**. Continuation

| Essential oil | Participants (diagnosis, *n*) | Results | References |
|---|---|---|---|
| Roman chamomile *(Chamaemelum nobile)* | Alteration of depressive- like behavior WKY rats (genetic depressive model) | Antidepressant effect. | Yingying KOng et al. (2017) |
| Sandalwood *(Santalum paniculatum)* | Murine model | Sedative effect but not anxiolytic-like activity. | Tadaaki et al. (2015) |
| Bitter Orange *(Citrus aurantium)* | Murine model | Improve anxiety and obsessive-compulsive disorder. | Moraes Pultrini et al. (2006) |
| Korean fir *(Abies koreana)* | Influence of binasal and uninasal inhalations in EEG activity in humans (n=20) | The binasal inhalation of *Abis koreana* increases the relaxation and the uninasal increases the alertness and attention state of human brain. | Min Seo et al. (2016) |
| Ylang-Ylang *(Cananga odorata)* | Murine model | Both acute and chronic ylang-ylang essential oil exposure showed anxiolytic effect on the mice. | Zhang et al. (2016) |
| Tuberose or Azucena *(Polianthes tuberosa)* | Anxiety among students (n=54) | Effective in reducing test anxiety among students. | Fereshteh et al. (2016) |
| Basil *(Ocimum basilicum)* | Murine model of depression. | Antidepressant-like effect. | Ali et al. (2017) |
| Angelica *(Angelica sylvestris)* | Murine model | Anxiolytic-like effect. | Si et al. (2004) |
| Indian cassia *(Cinnamomum tamala)* | Murine model | Anxiolytic, antidepressant, and antistress activitity. | Upadhyay et al. (2016) |
| Coriander *(Coriandrum sativum)* | Murine Model of anxiety | Anti-anxiety activity. | Mahendra and Bisht (2011) |
| Mugwort *(Artemisia indica)* | Murine Model | Anxiolytic and Antidepressant Activities. | Khan et al. (2016) |
| Japanese Spicebush *(Lindera obtusiloba)* | Murine model | Antidepressant-Like Effects. | Lim et al. (2016) |
| Sage *(Salvia officinalis)* | Healthy young participants. (n=30). Double-blind, placebo-controlled, crossover study. | The results confirm previous observations of the cholinesterase inhibiting properties of *S. officinalis*, and improved mood and cognitive performance following the administration of single doses to healthy young participants. | Kennedy et al. (2006) |
| Vetiver (*Chrysopogon zizanioides*) | Anxiety-related behavioural murine Model. | Anxiolytic properties of Vetiver essential oil might be associated with altering neuronal activation in central amygdaloid nucleus. | Saiyudthon et al. (2015) |
| Fennel *(Foeniculum vulgare)* | Postmenopausal women (n=90) Triple-blind, placebo-controlled trial. Murine model | Reduce menopausal symptoms.<br>Anxiolytic properties. | Rahimikian et al. (2017)<br>Mesfin et al. (2014) |