

*Invited Review***ESSENTIAL OILS AS MODIFIERS OF HUMAN BEHAVIOR<sup>1</sup>****[ACEITES ESENCIALES COMO MODIFICADORES DEL COMPORTAMIENTO HUMANO]**

**María Andrea Castillo<sup>1,2</sup>, Yenddy Carrero<sup>3</sup>, Kendy Eduardo Urdaneta<sup>1,2,4</sup>, Mathieu Renouf<sup>3,5</sup>, Charly Lubin<sup>3,5</sup>, Montiel Nola<sup>2</sup> and Neomar Semprún-Hernández<sup>1,2,3,\*</sup>**

<sup>1</sup> *Research Division, Autism Immunology Unit of Maracaibo, 4001, Maracaibo, Venezuela. Email: neomar.semprun@gmail.com*

<sup>2</sup> *Cátedra Libre de Autismo, Vicerrectorado Académico, Universidad del Zulia, 4001, Maracaibo, Venezuela*

<sup>3</sup> *Laboratorio de Biología Molecular y Celular. Facultad de Ciencias de la Salud. Universidad Técnica de Ambato. Ambato-Ecuador*

<sup>4</sup> *Departamento de Biología, Facultad Experimental de Ciencias, Universidad del Zulia, Maracaibo, Venezuela*

<sup>5</sup> *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

<sup>1</sup> Submitted May 22, 2017 – Accepted August 20, 2017. This work is licensed under a [Creative Commons Attribution 4.0 International License](https://creativecommons.org/licenses/by/4.0/)

## 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 are hypericin, 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 Rebueta 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 single doses of a range from 300-1800mg of Hp extract (0.3% of hypericin), hypericin was detectable in the blood after 1.3h, and peak plasma concentrations were reached after ~4.6 h and steady-state levels by 4 days (Staffeldt et al., 1994; Brochmoller et al., 1997; Upton, 1997). The plasma half-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's half-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 monoamine oxidase (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 no MAO 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, GABA<sub>A</sub>, GABA<sub>B</sub>, 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-HT<sub>2</sub> receptors in rat frontal cortex (Muller et al., 1997). Hyperforin has been shown to

be an uptake inhibitor of 5-HT, dopamine, norepinephrine, GABA and L-glutamate in 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 may be secondary to activation of the Na<sup>+</sup>/H<sup>+</sup> 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 (Hosseini 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 adrenocorticotrophic 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 its 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 (Aguirell 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-arachidonylethanolamine (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 which has a presynaptic 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).  $\Delta^9$ -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 it possesses 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 doses 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 neurological disorders, are studied on the field of endocannabinoid 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 marijuana for migraines and headaches have been described with positive findings (Clendinning, 1843; Greene, 1872; Osler and McCrae, 1915; McGeeney, 2013).

The doses in those studies were administered 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, adrenocorticotrophic 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 O<sub>2</sub>- 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. europaea*.

**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 nutrients 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).

Moreover, 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 A $\beta$  peptides and tau protein in AD, tau protein in other tauopathies (e.g. frontotemporal dementia),  $\alpha$ -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 A $\beta$  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 A $\beta$  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 A $\beta$ 40/42 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 mice, 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  $\gamma$ -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-HT<sub>5A</sub> which is implicated in the sleep-wake cycle (Dietz et al., 2005). In 2 randomized studies, (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  $\gamma$ -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, valeranal 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.

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

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

**Table 1.** Continuation

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