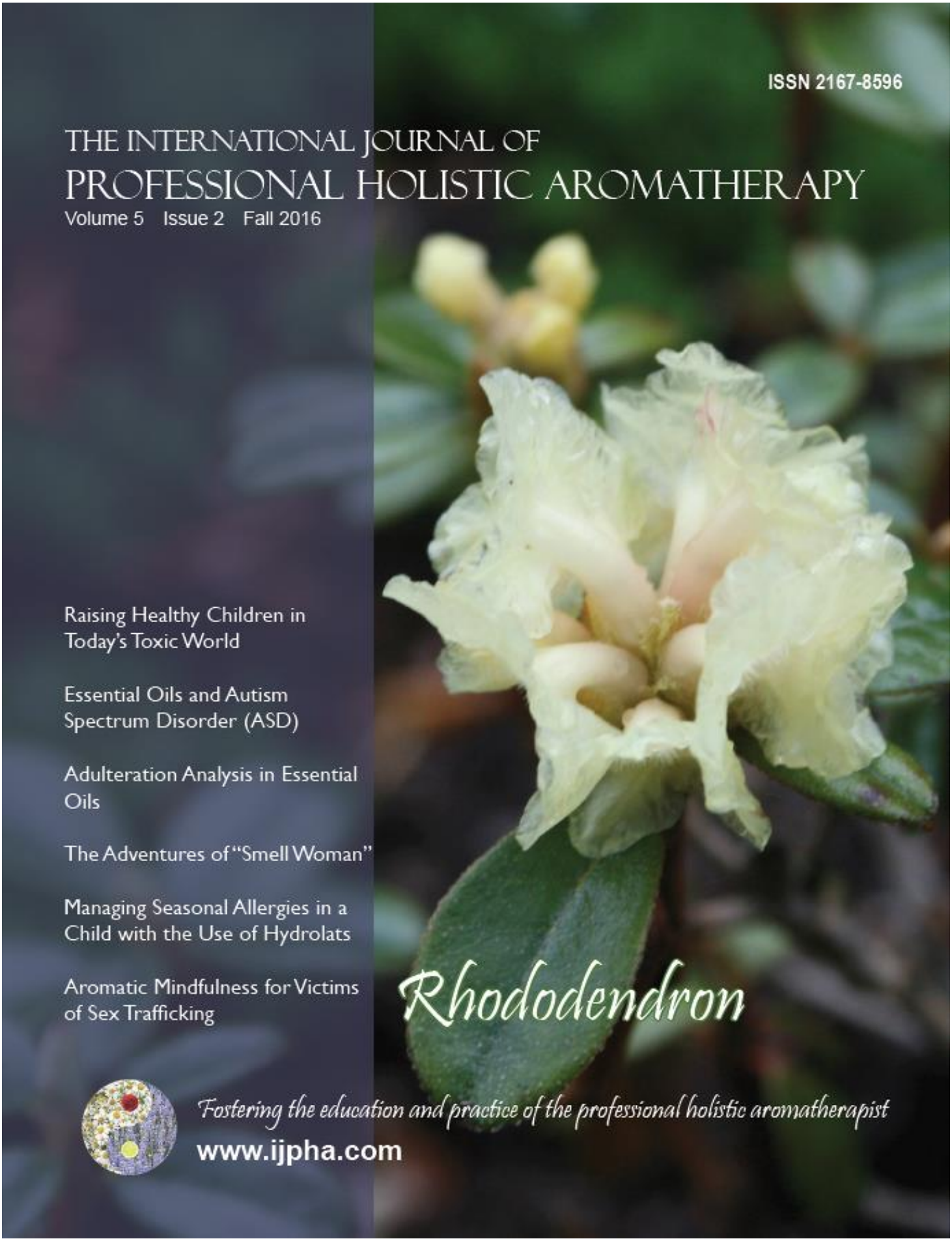
Essential Oils and Autism Spectrum Disorder (ASD)

Article · August 2016

ISSN 2167-8596

THE INTERNATIONAL JOURNAL OF PROFESSIONAL HOLISTIC AROMATHERAPY

Volume 5 Issue 2 Fall 2016



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Essential Oils and Autism Spectrum Disorder (ASD)

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Autistic child stacking cans © Nancy J. Price

Introduction

Autism spectrum disorder (ASD) is a group of pervasive neurodevelopmental highly heritable disorders developing in those under three years of age and is more common in boys than girls. It is common in children with clinically and genetically heterogeneous neurodevelopmental conditions causing impairments of verbal and non-verbal communication and social skills, stereotyped patterns of behavior, diminished ability to learn accompanied by epilepsy, gastrointestinal problems, compromised immune system, motor deficits, anxiety and mental retardation (Kanner, 1943; McCarthy *et al.*, 2010). Anxiety and epilepsy are often associated with autism, and seizures occur in up to 44% of individuals. Mental retardation reaches 60% and 30% respectively in individuals with autism and broader autism spectrum disorders (ASDs), respectively (Lecavalier, 2006; Fombonne, 2006; Tuchman and Rapin, 2002; McCarthy *et al.*, 2010).

ASD basically refers to a group of diseases: autistic disorder (autism, classic autism, Kanner's syndrome, AD), PDD-NOS (pervasive developmental disorder) (Reichow *et al.*, 2008), childhood disintegrative disorder (CDD) (Sri Hari Charan, 2012), Rett syndrome (Downs *et al.*, 2016), Williams-Beuren syndrome (Tordjman and Anderson, 2012), and Asperger's disorder (also called AS, Asperger's syndrome) (Lehnhardt, *et al.*, 2013).

Autism image
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Fig. 1. Complexity of autistic spectrum disorder, which is usually accompanied by a variety of syndromes, and physical and intellectual difficulties. © Dr. M. Emerald, 2016

ASD is officially recognized according to its subtype. In the early ("infantile") subtype of ASD, which is also characterised as "classical," symptoms begin in early infancy (Kanner and Eisenberg, 1957). Diagnosis of autism, through behavioral observation and psychological tests, could be complicated by other medical conditions for children under the age of one or two years (Dietz *et al.*, 2006) and is not precise. The most accurate diagnostics are available for children after 30 months (87%) (Turner *et al.*, 2006). The second subtype of ASD is known as "regressive" and development is normal until usually 18-36 months of age, but there could be some indications of onset ASD symptoms present even earlier (Kanner and Eisenberg, 1957).

The occurrence of ASD in the United States was 1 in 50 in 2011-12. Fifteen to twenty percent of adults with autism require community support (Baird *et al.*, 2003).

Potential causes of ASD

ASD has been researched intensively for over 30 years, but the question still remains unanswered as to whether autism is a result of a variety of causes including neuropathologies and genetic predisposition or whether a single pathology or cause can explain the full spectrum. There is a variety of different hypotheses that attempt to explain the real cause of autism including environmental factors (including heavy metals, pollutants and chemicals), genetic predisposition, nutritional deficiency, neurophysiological factors, anatomical pathology, and others.

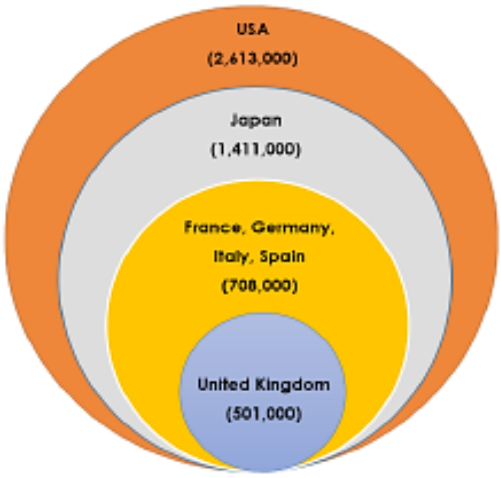


Fig. 2. Prevalence of autistic spectrum disorder (ASD) in different countries (adapted from Nightingale, 2012). © Dr. M. Emerald 2016.

Autism: environmental factors and heavy metals

ASD involves systemic physiological abnormalities, and until recently the importance of environmental toxins in development of such systemic abnormalities was basically neglected. Environmental factors are proven to make a significant contribution to the rise and development of autism (Kubota *et al.*, 2012). Exposure to environmental toxins (Rossignol *et al.*, 2014) such as mercury, lead, arsenic, polychlorinated biphenyls (PCBs) and toluene are well-known causes of many neurodevelopmental disorders. In addition to the huge genetic heterogeneity in ASD (about 55%) (Hallmayer *et al.*, 2011), environmental pollutants (such as pesticides, phthalates, PCBs, solvents, heavy metals, air pollutants and others) have been found to be able to induce the epigenetic alterations with typical DNA methylation patterns ("environmental footprints"), which could be trans-generational in nature and might potentially trigger development of cancer, neurodegenerative disorders, autoimmune disorders, among others (Baccarelli and Bollati, 2009; Salnikow and Zhitkovich, 2008).

The first histopathological evidence of pollution influence in animals was a post-mortem study on canines exposed to air pollutants, which caused inflammation, neurodegeneration, and DNA damage in the brain (Calderón-Garcidueñas *et al.*, 2002; Calderón-Garcidueñas *et al.*, 2003). Inhaled pollutants absorbed by the olfactory epithelium, and also those that stimulate sensory afferents in the gastrointestinal tract, cause neuroinflammation, oxidative stress, glial activation, and injury (Block and Calderón-Garcidueñas, 2009). Exposure to environmental tobacco smoke, chemicals and traffic noise have also been associated with impaired cognitive development (Clark *et al.*, 2012). Animal and human studies support the hypothesis that males could be more susceptible to air pollution neurotoxicity (Curtis *et al.*, 2010). The susceptibilities to toxicants, which are affected by genetic factors, oxidative stress, altered neuronal development and synaptic function, and impaired hormonal factors, could act synergistically and amplify the adverse effects of toxicants during critical periods of neurodevelopment, particularly during the prenatal period (Rauh *et al.*, 2006). Studies suggest a potential association between pollution (PAH, PM2.5, and NOx), and neuropsychological development in children, which can lead to the development of autism and other neurodegenerative diseases. There is evidence to support the link between exposure to agricultural pesticides, especially chlorpyrifos during the period of nervous system organogenesis, and the causation of autism in newborns (Landrigan, 2010; Roberts *et al.*, 2007); however, more research is needed. According to a number of other studies, significant difference has been found in hair levels of arsenic, cadmium, barium, cerium, antimony, uranium and lead between an autistic group and a control group of children (Fido and Al-Saad, 2005). Prenatal exposure to pharmacological agents and prescription drugs, and especially thalidomide and VPA, are among the well-known environmental risk factors contributing to the risk of autism and neurodegenerative disorders (Becker and Schultz, 2010). VPA exposure produces distraction of motor performance and social behavior, and changes in postnatal development (Narita *et al.*, 2010; Schneider and Przewłocki, 2005).

Autism and nutritional deficiency

It has been shown that children with autism have impaired methylation, decreased glutathione levels and a high level of oxidative stress (Chauhan and Chauhan,

2006), and treatment with vitamin methyl-B_{12} and trimethylglycine has been found to be beneficial. According to some studies patients with autism have a 10% higher level of copper, and lower levels of iodine, lithium, and vitamins A, E and D (WHO, 2007; Anke *et al.*, 1991; Krajkovicova-Kudlackova *et al.*, 2009; Duignan *et al.*, 2015). Calcium deficiency usually elevates lead accumulation causing impairment of cognitive development. Iron deficiency increases absorption of cadmium, lead, and aluminum (Goyer, 1997). The abnormalities found in ASD patients with deficiencies of vitamins, amino acids and minerals (Sathyanarayana Rao *et al.*, 2008), and especially decreased tryptophan metabolism in cells, have been shown to lead to decreased levels of serotonin in the brain which may explain repetitive behaviors (spinning, stepping, self-hitting) (Boccuto *et al.*, 2013).

Ophthalmic manifestations of vitamin A and D deficiencies decreased levels of plasma ATP causing decreased endurance in children with autism (Duignan *et al.*, 2015), lower levels of plasma tryptophan, increased plasma glutamate, and lower levels of several other amino acids (James *et al.*, 2004). Research supports a link between autism and nutritional and metabolic biomarkers, but more research and clinical studies are needed to evaluate whether these biomarkers can be considered reliable markers of ASD (Esparham *et al.*, 2015). However, use of nutraceutical supplements and inclusion of an abundance of greens in the everyday diet of patients with autism offer great benefits including body detoxification, enhancing the immune system, and diminishing cellular stress and the level of the environmental toxin accumulation.

Autism and gut microbiota

Strong correlation has been found between gastrointestinal (GI) dysbiosis and a variety of pathological conditions including autoimmune disorders, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), psychiatric disorders and autism (Fond *et al.*, 2015). Neuropeptides, especially 36 amino acid neuropeptide Y (NPY), peptide YY, vasoactive intestinal polypeptide, somatostatin and corticotropin-releasing factor, all play a crucial role in proper coordination of the microbiota-gut-brain axis (Thakur *et al.*, 2014). The NPY controls the gut microbiota influence on pain and inflammatory processes, behavioural patterns and brain functions, as well as the level of brain metabolites. The gut microbiota is able to not only communicate through the activation of gastrointestinal epithelial, and immune and neuronal pathways, but also release special molecules able to signal to many organs and brain centres via microbial metabolites discovered in the blood stream and actively involved in system blood circulation (Bercik *et al.*, 2011). The changes in gut microbiota affect the human brain through the activation of the hypothalamus pituitary-adrenal (HPA) axis (Cryan and Dinan, 2012). ASD is often associated with a variety of gastrointestinal problems, such as abdominal pain and constipation/diarrhea, decreased ability to concentrate, behavior problems, and self-abuse. The levels of *Clostridium* species, especially *Clostridium histolyticum* and *Clostridium difficile*, *Bacteroides*, *Ruminococcus* species, and others were higher in ASD patients than in control studies. *Sutterella*, *Prevotella*, and *Alcaligenaceae* family species have been found to be altered as well (Finegold *et al.*, 2010; Kang *et al.*, 2013; Wang *et al.*, 2013). Children with autism had lower levels of *Bifidobacterium* and *Enterococcus*, higher levels of *Lactobacillus*, and were more likely to have *Bacillus* spp. and less likely to have *Klebsiella oxytoca* (Adams *et al.*, 2011) in the GI tract. About 43% of children with autism have shown positive fungal culture or yeast (Horvath and Perman, 2002). The gut microbiota is crucial for maturation of the immune system through stimulation of local and systemic immune responses (Nell *et al.*, 2010). The implementation of different bacteria, such as a combination of *L. helveticus* and *B. longum*, have an anxiolytic-like activity in rats, and daily administration reduces psychological distress (Messaoudi *et al.*, 2011). The daily administration of *Lactobacillus casei* improves anxiety-related symptoms (Jiang *et al.*, 2015). The application of proper gut microbiota modulators could be crucial for the understanding and maintenance of ASD and mood disorders.

Viral infection, cytokines and autism

According to a recent study, incidence of autism is now 1 in 68 in children in the United States and is more prevalent in boys than girls (Esparham *et al.*, 2015). One hypothesis for the cause of autism is early infantile viral infections which attack the CNS of underdeveloped infants (Rosenberger, 1975). Several studies performed on humans suggest correlation between maternal viral infection during a mother's pregnancy and risk of ASD development in

newborns. The herpes simplex virus 1 and 2 (HSV 1 and 2), human herpes virus 6 (HHV-6), Epstein-Barr virus, rubella virus, measles virus and cytomegalovirus are among the most possible viral factors leading to development of autism in the fetus. The outcome of prenatal viral infection is dependent on the mother's immune system, type and strain of the virus, the amount of virus reaching the fetus's nervous and immune system, and genetics (Hutton, 2016). The infant's immune response causes the production of cytokines (interleukin (IL)-1, -2, and -6), which can significantly affect the release of dopamine, acetylcholine, serotonin, and norepinephrine in different regions of brain (Hanisch *et al.,* 1993).

A mother's infection might cause an increase in the level of cytokines in the fetus without viral persistence, and can cause elevated cytokine production in the brain or via the blood-brain barrier (BBB). There are a variety of studies trying to associate autism with viral infections; for example, association of human parvovirus and herpes simplex virus (HSV) with infantile autism (Anlar *et al.*, 1994). Gregg (1941) and Desmond *et al.* (1970) proposed that rubella virus contributes to autism, which was later supported by studies performed by Chess (1971; 1977). A few reports link cytomegalovirus (CMV) infection (herpes virus family member) with autism (Markowitz, 1983). Herpes viruses have been shown to stimulate production of proinflammatory cytokines with elevated IFN in the brain during HSV encephalitis (Legaspi *et al.*, 1980). Autistic children have shown significantly higher levels of anti–measles-mumps-rubella antibodies than normal children (Singh and Jensen, 2003). Disbalance of Th1/Th2 cytokines and elevated levels of plasma IL-12 and IFN-gamma could be linked to the pathogenesis of autism. Genetic alterations, autoimmunity, viral infections, maternal/fetal immune interactions, injuries and ischemia on the levels of circulating cytokines may be one explanation for the development of ASD.

Autism, brain structures, neurotransmitters and signaling pathways

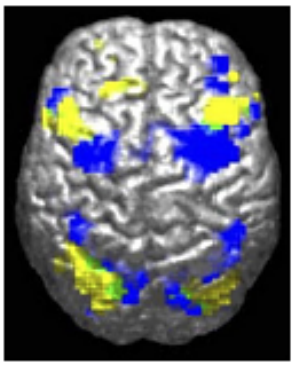
Pathological changes in brain structure and connectivity in regions of the brain are found in patients with ASD. It is well known that the cerebellum is the region of the brain that is connected with different regions of cerebral cortex, controlling sensing, movement, social processing, motivation, attention, memory, language, and execution (Snider and Maiti, 1976; Kellermann *et al.*, 2012; Snider and Stowell, 1944; Schmahmann and Pandya, 1997; Kelly and Strick, 2003; Snider and Eldred, 1951; Heath and Harper, 1974; Middleton and Strick, 2000). A potential link between autism and atrophied Purkinje cells (the primary output neurons of the cerebellar cortex and cerebellum) has been discovered (Fatemi *et al.*, 2002). Reduced Purkinje cell size has been found to cause impaired performance on the serial reversal learning tasks (Dickson *et al.*, 2010; Martin *et al.*, 2010). A hypothesis based on electrophysiological findings describes a rise in occurrences of autism as a result of the site-specific impairment of the *nucleus tractus* solitarius (NTS) (McGinnis *et al.*, 2013), and impaired flow of viscerosensory information to the higher centers, via the ascending noradrenergic system.

Neurotransmitter systems have been shown to be responsible for the neurophysiological misbalance associated with the pathogenesis of GABAergic, glutamatergic and serotonergic systems, as well as depletion of the catecholamines and acetylcholine in patients with ASD. Studies have found that in the cerebellum and parietal cortex of patients with ASD there is a significant decrease in the enzyme responsible for the conversion of glutamate to GABA, which caused a reduction of GABAA and GABAB receptor subunits in various brain regions, which in turn can lead to hyperexcitability and cognitive dysfunction (Blatt *et al.*, 2001; Fatemi *et al.*, 2010; Olmos-Serrano *et al.*, 2010). The mutations of genes in some of the GABAA receptors could be the main cause of the reduction in GABAergic transmission (Coghlan *et al.*, 2012; Jamain and Betancur, 2002). Brain maturation, synaptogenesis and neuroplastisicity are dependent upon an optimum glutamate transmission level. A high level of glutamate causes overstimulation of NMDA receptors, and an increase of calcium influx leading to the neuronal damage also found in a number of ASD patients. The hypothesis that NMDAR dysfunction can lead to changes in neuroplasticity, neuronal circuits, and corresponding behaviors must be researched and analyzed in depth (Lee *et al.*, 2015; Pilpel *et al.*, 2009). Using NMDA receptor antagonists in clinical practice has

Synapse in brain, aboutmodafinil.com

significant positive impact on focus and attention in ASD patients (Muehlmann and Devine, 2008).

The prefrontal and temporal cortex serotonin system, which is responsible for GABA inhibition, plays a crucial role in the regulation of many aspects of cognitive function and development of social skills during the earliest years of development. A variety of studies demonstrate that ASD patients' serotonin levels are significantly changed in various brain regions (frontal cortex, cingulate, and thalamus) (Adamsen *et al.*, 2014; Nakamura *et al.*, 2010). There are just a few antipsychotic drugs, such as risperidone and aripiprazole, allowed for the treatment of irritable and aggressive behaviors in kids with autism (West and Waldrop, 2006; Blankenship *et al.*, 2010).



fMRI-derived image of difference between brains of autistic (yellow) and control (blue) groups. ©Ralph-Axel Müller

People with autism spectrum disorders (ASD) are often impaired across a range of cognitive tasks, including adapting behavior, generation of novel behaviors and ideas, and planning, all of which are associated with executive functioning. The executive dysfunction (ED) theory of autism attempts to explain the mechanism which is behind the failure of executive control over behavior. There are various cognitive impairments found to be connected to the cerebellar pathology and dysfunction within posterior lobules VI-VIII, which include, but are not limited to, deficit of control and attention, language and memory impairment, and change in dopamine release in the prefrontal cortex controlled by the cerebellum (Rogers *et al.*, 2011; Mittleman *et al.*, 2008).

Reduced norepinephrine and increased dopamine levels in the orbitofrontal cortex region, as well increased catecholamine levels in the blood, urine, and cerebrospinal fluid, were found in ASD patients (Martineau *et al.*, 1994; Ernst *et al.*, 1997). In a few studies it has been found that variation in dopamine transporters (DAT), dopamine receptors, and/or catechol-O-methyl transferase (COMT) genes play an important role in development of ADHD, which is a part of the wider picture of autism. It has been found that dopamine transporter (DAT) expression removal decreases presynaptic dopamine and stimulates hyperactivity (Kim *et al.*, 2014).

Disturbances of dopaminergic transmission on many levels are typical for autism, Parkinson's, Alzheimer's, ADHD, and ASD.

ASD and the autonomic nervous system

ASD is also associated with significant abnormalities of the autonomic nervous system. There are disturbances with the transmission of autonomic signals in multiple areas of the brain (such as the thalamus, amygdala, nucleus accumbens, reticular formation, hypothalamus and others) (Critchley *et al.*, 2011), which are involved in regulation of autonomic functions and emotional states (Kushki *et al.*, 2014; Amaral and Corbett, 2003; Kleinhans *et al.*, 2010; Haznedar *et al.*, 2000).

Autism and olfactory processing

Studies among children with ASD demonstrate abnormal responses to odors and tastes, including cold, heat, pain, tickle, and itch (Rogers *et al.*, 2003; Legisa *et al.*, 2013; Kientz and Dunn, 1997). The impaired amygdala function in ASD patients may explain abnormal evaluation of unpleasant odors as more unpleasant compared to the control group (Royet *et al.*, 2003). A variety of olfactory tests performed with ASD patients show dysfunction of different levels of processing information, which involved different brain regions having anatomical and functional abnormalities (Anagnostou and Taylor, 2011).

Autism and essential oils

There are a few essential oils that could be quite helpful for symptoms of ADHD, anxiety, over excitation, depression, sleeping problems, and seizures typically found in patients with ASD. Some essential oils extracted from Vietnamese Balm (*Elsholtzia ciliata*), Korean Angelica (*Angelicae gigantis* Radix), and Clove (*Syzygium aromaticum*) can modulate the dopamine system and effectively induce hyperphosphorylation of cyclic-AMP response element-binding protein (CREB), MAPK, and AKT, which result in DAT upregulation (Choi *et al.*, 2015). Chaste tree (*Vitex agnus castus*) essential oil contains diterpenes with pharmacological dopaminergic activity, acting as dopaminergic agonists, affecting the D2 receptors (Sorensen, 2000; 2001). The antidepressant action of Clary Sage (*Salvia sclarea*) essential oil is also associ-

ated with the regulation of the dopaminergic pathways (Seol *et al.*, 2010). Cannabis (*Cannabis sativa*) essential oil, and its compound Δ9-tetrahydrocannabinol, increases dopamine concentrations in terminal regions of the mesolimbic dopamine system (Di Chiara and Imperato, 1988; Pierce and Kumaresan, 2006).

Vetiver essential oil

The name *Vetiveria* comes from the Tamil word "vétiver" ("root that is dug up"), and *zizanioides* (meaning "by the riverside"), and was first used by Carolus Linnaeus (Sweden) in1771 (Vietmeyer and Ruskin, 1993). The other common names for Vetiver are Vetivert, Ruh Khus, Khas-Vetiverol, Khas or "oil of tranquillity." Vetiver belongs to the Poaceae family (*Vetiveria zizanioides* or *Chrysopogon zizanioides*) and is found in Vietnam and India. It is also cultivated in Haiti, Reunion Islands, Thailand, Australia (Queensland and Northern Territory) and other countries (Thakur *et al.*, 1989). Vetiver (*Vetiveria elongata*, *Vetiveria pauciflora*, *Vetiveria intermedia* and *Vetiveria filipes*) is a tall perennial grass plant with highly aromatic roots and is valued for its wide range of therapeutic properties. There are differences in Vetiver essential oil obtained from different geographic regions of the world with regard to quality and perfumery notes. Essential oil distilled from Vetiver roots via hydro-distillation, steam distillation, solvent extraction or supercritical fluid extraction (Danha *et al.*, 2010) contains sesquiterpenoids, hydrocarbons, tannins, phenols, terpenoids, and saponins, and consists of more than 156 bioactive compounds (Bhuiyan *et al.*, 2008). The main components of the Vetiver essential oil (India) are: eudesma-4,6-diene (δ-selinene) + β-vetispirene (3.9-6.1%), β-vetivenene (0.9-9.4%), and 13-nor-trans-eudesma-4(15),7-dien-11-one + amorph-4-en-10-ol (5.0-6.4%).

Vetiver extracts and essential oil are used for epilepsy, fever, headache, hyper acidity, ulcers, and urinary tract infection, and they possess analgesic, anthelmintic, antifungal, antimicrobial (phenolic acids inhibit gram positive partially and gram-negative bacteria), and antioxidant activity (Subhadradevi *et al.*, 2010), as well as antihyperglycaemic, anti-inflammatory, antipyretic, and powerful sedative properties (Luqman, 2005, 2012; Karan *et al.*, 2010; Subhadradevi *et al.*, 2010; Chen *et al.*, 2003; Narkhede *et al.*, 2012; Basuri and Vishal, 2011; Karan, 2013). Anxiety disorders, which are always an important element of the ASD clinical picture, have a high negative impact on daily life and cause tremendous suffering to the patient and family members (Chansky, 2004; Sadock and Sadock, 2007). Anxiety is a condition involving fears, learning difficulties, nervousness, stress, unbalance and worry often accompanied by headache, palpitations, perspiration, stomach cramps, and tightness in the chest. Extensive research suggests that plant flavonoids, which are also found in Vetiver oil, play an important protective role in various neurodegenerative diseases including anxiety and cognitive impairment typical for ASD patients. Vetiver essential oil distilled from the root, as well as Vetiver extract, were reported to have strong anxiolytic and nootropic activity (to enhance memory or other cognitive function) in mice (Luqman, 2012). Inhalation of Vetiver essential oil volatiles in rats has shown significant sedative effect. Vetiver is traditionally used in Aromatherapy for relieving anxiety, insomnia, nervous tension and stress (Fischer-Rizzi, 1990). The anxiolytic properties of Vetiver essential oil could be associated with altering neuronal activation in the central amygdaloid nucleus (CeL) (Saiyudthong *et al.*, 2015). Inhalation of low doses of Vetiver oil by humans has shown to decrease the activity of the sympathetic nervous system and cause a general sedative effect on brain activity relieving stress, anxiety, nervous tension and insomnia (Saiyudthong *et al.*, 2015), which could be helpful for patients with ASD.

Wild Basil essential oil

Wild Basil (*Ocimum gratissimum*) is a small shrub also known as Tea Bush, African Basil, Clove Basil, Nchanwu plan (Nigeria), Ram Tulsi (Hindi), and Vriddhutulsi (Sanskrit). It belongs to the plant family Labiatae and is cultivated in Ceylon, South Sea Islands, and also within Nepal, Bengal, Chittagong, and Deccan (Nadkarni, 1999). In West Africa and India, *O. gratissimum* is often found in gardens and used to flavor soup and meat (Iwu, 1993); in Indonesia (Sumatra) its leaves are used for preparation of fresh tea; and in Thailand the leaves are used as a natural food flavouring. In everyday life, villagers from West Africa use plant teas, decoctions, extracts and essential oil. The fresh leaves of *O. gratissimum* contain about 0.8-1.2% essential oil and possess strong antifungal (Terezinha *et al.*, 2006), antioxidant (Joshi, 2013), antiseptic (Kabir *et al.*, 2005), and sedative (Cristiana *et al.*, 2006) properties. *O.gratissimum* is also used as an effective anti-inflammatory (Sahouo *et al.*, 2003) and cardioprotective

(Lahlou *et al.*, 2004). *O. gratissimum* is used for the treatment of catarrh (Ijeh *et al.*, 2005), conjunctivitis (García *et al.*, 1998), diabetes (Mohammed *et al.*, 2007), epilepsy and high fever (Effraim *et al.*, 2003), mental illness (Akinmoladun *et al.*, 2007), respiratory tract infection (Matasyoh et al., 2007), skin problems (García *et al.*, 1998), soothing abdominal pain, stomach upset and haemorrhoids (Kabir *et al.*, 2005). Eugenol derived from *O. gratissimum* is an important therapeutic component which could be the main player in protection against oxidative stress (Bozin *et al.*, 2006). Eugenol's anticonvulsant activity when administered intra-peritoneally (i.p.) before seizure is well known. But the anti-epileptic activity of essential oils containing eugenol, and *O. gratissimum* in particular, could be explained by interactions with other compounds, such as sesquiterpenes like β-eudesmol (Chiou *et al.*, 1997).

Several chemotypes of *Ocimum gratissimum* have been identified including; eugenol, geraniol, methyl cinnamate, methyl eugenol, and thymol (Benitez *et al.*, 2009; Charles and Simon, 1992; Gildemeister and Hoffmann, 1961; Orwa *et al.*, 2009). Composition of *O. gratissimum* essential oil varies geographically and on the time of the year it is harvested. For example, African *O. gratissimum* essential oil is rich in eugenol (10.7%), an anesthetic, anticonvulsant, and myorelaxant (Dallmeier and Carlini, 1981), thymol (35-40%), and *para*-cymene (18.30%) (Ntezurubanza *et al.*, 1987). *O. gratissimum* essential oil distilled from plants grown in Albania were found to consist of 67-73% eugenol whereas the *O. gratissimum* essential oil distilled from plants found in Georgia (former Republic of USSR) contained 54-94% eugenol. The *O. gratissimum* essential oil from Vietnam was found to contain up to 71% eugenol, with small amounts of *d*-germacrene and (Z)-β-ocimene. *O. gratissimum* from southern China contained 95% eugenol, while *O. gratissimum* from Madagascar ranged from 40 to 90% (Haki, 1970). *O. gratissimum* distilled from Brazil, Russia and other parts of Europe contained the highest percentage of eugenol (Pressoa *et al.*, 2002). The highest amount of eugenol was detected in the *O. gratissimum* essential oil during the autumn season (Dallmeier and Carlini, 1981).

Ocimum gratissimum © Forest & Kim Starr/Wiki Commons

The greatest sedative effect was detected in the thymol chemotype of *O. gratissimum* essential oil (Orafidiya *et al.*, 2004). The *O. gratissimum* essential oil distilled from African regions contained the highest percentage of thymol (Ngasoum *et al.*, 2003).

The cinnamate chemotype of *O. gratissimum* plants are cultivated or wild grown in India and Pakistan (Dubey *et al.*, 2000). There is a geraniol-rich (84-88%) type with small amounts of γ-muurolene, neral, β-caryophyllene and limonene (Orwa *et al.*, 2009). *O. gratissimum* essential oil containing a high thymol and *para*-cymene content and free of eugenol or 1,8-cineole demonstrated a strong sedative effect in experiments on mice (Orafidiya *et al.*, 2004). The presence of linalool (Edewor-Kuponiyi, 2013), myrcene (Vale *et al.*, 2002), and other compounds founds in *O. gratissimum* essential oil also demonstrate sedative and anticonvulsant effects (Aggarwal and Mishra, 2004).

Conclusion

Autism spectrum disorders (ASD) represent a variety of diseases with complex multi-level psychological dysfunctions, and physiological and molecular pathogenesis. Autism is recently being recognized as an important health issue in many countries all over the world. The common cause of ASD has not yet been discovered; however, there are multiple studies that target environmental, gastrointestinal, genetic, microbiological, nutritional, toxicological and other factors which could possibly trigger development of ASD at an early age. There are essential oils which can be used to soothe different symptoms such as anxiety, depression, and insomnia. More research and clinical studies need to be done to determine the exact cellular and molecular mechanism of essential oil action on the circulatory, digestive, lymphatic, and nervous systems and their proper use in the treatment of the symptoms associated with autism.

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