



ISSN: 0975-833X

Available online at <http://www.journalcra.com>

INTERNATIONAL JOURNAL  
OF CURRENT RESEARCH

*International Journal of Current Research*  
Vol. 13, Issue, 12, pp.19767-19771, December, 2021

DOI: <https://doi.org/10.24941/ijcr.42292.12.2021>

## RESEARCH ARTICLE

# AROMA OILS FOR THE AILMENT OF DEMENTIA: A REVIEW

Nissy P Jacob and Dr. Krishna Ravi\*

Department of Pharmacy Practice, J.K.K. Nattraja College of Pharmacy, Kumarapalayam-638183, Tamil Nadu

### ARTICLE INFO

#### Article History:

Received 25<sup>th</sup> September, 2021

Received in revised form

19<sup>th</sup> October, 2021

Accepted 10<sup>th</sup> November, 2021

Published online 29<sup>th</sup> December, 2021

#### Keywords

Aromatherapy, Dementia,  
Alzheimer's Disease,  
Essential Oils, Mood Disorders.

#### \*Corresponding author:

Dr. Krishna Ravi

### ABSTRACT

Aromatherapy has been used for thousands of years, but it has only recently gained popularity. Aromatherapy has been widely used for dementia but it is also found effective in treating various conditions like, mood disorders, menstrual issues, alopecia and pain. For therapeutic purposes, aromatherapy employs essential oils extracted from plants. The current review discussed the connection between dementia and Alzheimer's disease and also between the olfactory sense and dementia. This review also gives an insight into the mechanism and adverse effects of aromatherapy. Further information has been provided about the common plant essential oils which belongs to different family and its medicinal use. Even though aromatherapy is considered a promising alternative for many pharmacological medicines, more specific research is needed to understand the pharmacological mechanisms underlying aromatherapy before it can be widely used.

Copyright © 2021. Nissy P Jacob and Dr. Krishna Ravi. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Citation: Nissy P Jacob and Dr. Krishna Ravi "Aroma oils for the ailment of Dementia: A Review", 2021. *International Journal of Current Research*, 13, (12), 19767-19771.

## INTRODUCTION

Aromatherapy is made out of two words: aroma, which means fragrance or smell, and therapy, which implies treatment. This therapy is a natural way for a person's mind, body, and spirit to heal<sup>(1)</sup>, is a kind of phytotherapy that use essential oils collected from the various organs of aromatic plants and supplied through inhalation, topical application, or massage for a variety of minor clinical purposes. Aromatherapy has seen a significant increase in its usage as a treatment for a variety of illnesses, including anxiety, mood disorders, and certain types of pain<sup>(2)</sup>. For thousands of years, plant essential oils have been used in aromatherapy, and knowledge of essential oil distillation and application to promote general well-being and specific health concerns was brought to Europe as early as the 10th century<sup>(3)</sup>. According to a literature review, this therapy attracted a lot of attention in the late twentieth century and is still highly popular in the twenty-first century, and it is regarded as aroma science therapy because of its importance, popularity, and broad use<sup>(4)</sup>. Aromatherapy has the advantage of being less dangerous and more convenient to use than traditional treatments such as massage and baths. A number of plant species, including lemon balm, lavender, chamomile, bergamot, neroli, and valerian, have been used in medical herbalism for their alleged benefits on mental health issues<sup>(3)</sup>.

Furthermore, aromatherapy, in conjunction with psychological treatment, has provided the most evidence for the treatment of agitation in dementia patients<sup>(5)</sup>. Because of their supposed sedative and/or cognitive enhancing properties and, more recently, emerging supportive neurochemical and clinical studies, the essential oils of two Lamiaceae family species, *Melissa officinalis* L. (lemon balm) and *Lavandula officinalis* L. (lavender), are the most commonly used aroma therapeutic agents for the treatment of behavioural and psychological symptoms of dementia (BPSD)<sup>(6-8)</sup>. The mechanism of action of aromatic plant constituents is still unknown. The toxicity profiles of essential oils used in aromatherapy have been discovered to be extremely low, and using pure aromas has been found to be safe<sup>(9)</sup>.

**Use of Essential Oils:** For centuries, many cultures around the world have used essential oils for a variety of purposes, depending on the culture. It is unclear whether the EOs were initially used as healing agents or for domestic purposes<sup>(10-12)</sup>. There has recently been a surge in interest in the use of essential oils (EOs) in aromatherapy for their curative properties<sup>(13)</sup>. The main therapeutic agents in aromatherapy are essential oils, which are considered to be highly concentrated substances extracted from flowers, leaves, stalks, fruits, and roots, as well as resins<sup>(14)</sup>.

Essential oils are mostly made up of lipophilic, small, non-polar molecules. They are able to easily penetrate the skin and exert their effects there<sup>(15)</sup>. While the majority of clinicians believe that essential oil use is generally safe and would like to provide enough guidance regarding the application of essential oils, but they are not confident in their ability to do so<sup>(16)</sup>.

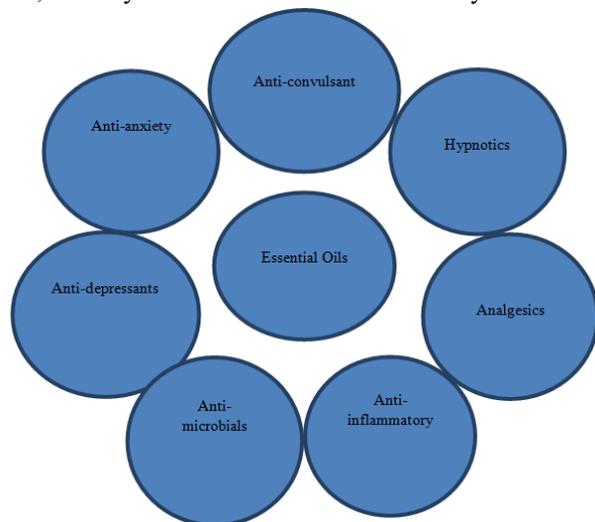


Figure 1. Effects of aromatherapy

For instance, in one study, mice were exposed to a mixture of lemon and rosemary aromatic essential oils in the morning, which are known to trigger the sympathetic nervous system, improving concentration and memory, and a mixture of lavender and orange oils, which stimulate the parasympathetic nervous system, calming the patients' nerves, in the evening. Furthermore, following treatment, the brain levels of amyloid beta ( $A\beta$ ), abnormally phosphorylated tau, and brain-derived neurotrophic factor (BDNF), a neurotrophic factor that promotes growth, survival, and differentiation in the brain<sup>(17)</sup>, were measured. The developed therapy significantly improved the cognitive function of dementia patients. These findings imply that aromatherapy using these aromatic essential oils can be beneficial in the prevention and treatment of Alzheimer's disease<sup>(18)</sup>. Personal use of essential oils was found to be positively correlated with the belief that there is a need for more training, research, and reimbursement for their use, as well as a desire to provide essential oil recommendations and receive formal certification in this modality.

#### Types of essential oils and it's medicinal use:

**Lavender Essential Oil:** Lavender essential oil is a transparent, white to pale yellow liquid with a distinctive odour that is extracted through steam distillation from the flowering tops of *Lavandula angustifolia* Mill. The oil's anti-inflammatory, calming, headache-relieving, sedative (used in sleep disorders), and skin-healing properties make it popular. One of the little-known effects or the outcome of using *L. angustifolia* oil is its ability to alleviate menstrual pain<sup>(19,20)</sup> along with its anxiolytic effects by inhibiting voltage-gated calcium channels primarily in hippocampal neurons.<sup>(21,22)</sup>

**Neroli Essential Oil:** The flower of *Citrus aurantium* var. *amara* L., also called bitter orange, is used to extract Neroli essential oil. Although the oil has antimicrobial<sup>(23)</sup>, antidepressant, antiseptic, carminative, antispasmodic, and sedative properties, it does contain allergens<sup>(24)</sup>.

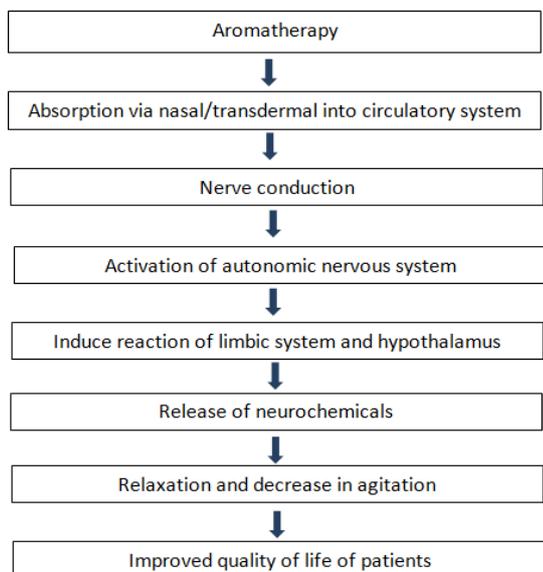
**Peppermint Essential Oil:** *Menthapiperita* L., a cross between watermint (*M. aquatic* L.) and spearmint, is used to produce peppermint essential oils (*M. spicata* L.). Peppermint oil can be taken orally as a dietary supplement for gastrointestinal complications in the medical setting<sup>(25,26)</sup>.

**Rosemary Essential Oil:** *Rosmarinus officinalis* L., also known as rosemary, is a fragrant plant in the Lamiaceae family. Rosemary essential oil is widely used in hair care because it nourishes the hair, promotes hair growth, and combats dandruff. It is also recommended for hair loss treatment because it is thought to perform a similar function to Minoxidil. Rosemary oil widens and opens blood vessels, increasing the availability of blood and nutrients to follicles, which are then stimulated to produce new hair<sup>(27)</sup>.

**Lemon balm oil:** *Melissa officinalis* L. (Lemon balm) is a Lamiaceae family member and a traditional medicinal plant which is well-known in the East Mediterranean region and West Asia<sup>(28)</sup>. *M. Officinalis* studies revealed that it improved agitation without causing significant side effects<sup>(29)</sup>.

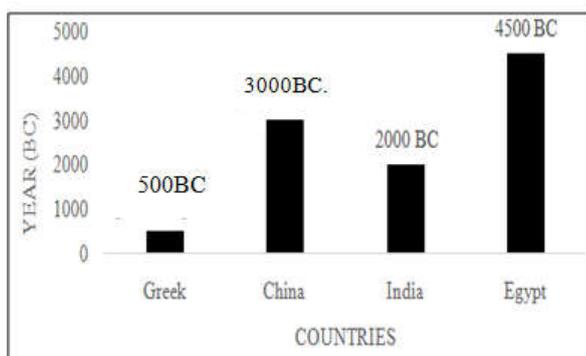
**How the therapy works:** Essential oils are administered in small amounts through a variety of methods, including inhalation, massage, or simple applications on the skin's surface, and they are rarely taken internally<sup>(30,31)</sup>. These essential oils act on olfactory nerves that run from the nose to the brain. Aromatherapy absorbs essential oils into the circulatory system through the skin when applied transdermally. The effect is caused primarily by nerve conduction. The peripheral nerves are stimulated first, followed by the somatic nerves and autonomic nerves. Somatic nerve stimulation causes skeletal muscles to relax, while sympathetic and parasympathetic nervous system stimulation causes blood vessels, internal organs, and glands to function<sup>(32)</sup>. According to some research, the most common symptoms of dementia, sleeplessness and agitation, are associated to the level of sympathetic nervous activity<sup>(33)</sup>. When the sympathetic nervous system is overactive, it causes an increase in plasma catecholamine levels and lower cognitive ability, as well as high blood pressure, agitation, and arrhythmia<sup>(34)</sup>, as well as possible inhibition of parasympathetic nervous activity. Aromatherapy's action begins with a smell molecule combined with an acceptor unique to each odour if it is applied through inhalation. The molecule of smell travels through the nasal cavity and adheres to the olfactory epithelium. The olfactory nerve system, which is presently concentrated on the olfactory epithelium, transmits the stimulus to the hippocampus or cerebral limbic system and amygdaloid body. Although this process is closely connected to cognitive function, the odour is recognised, and the stimulus sends information to the hypothalamus on which it was projected by the cerebral limbic system, which then adjusts the autonomic nervous system and the internal secretory system, guiding a series of vital reactions in the hippocampus or amygdaloid body, such as neurotransmitter discharge. In a nutshell, aromatherapy is the result of a vital reaction mediated by the smell molecule<sup>(35,36)</sup>.

**Adverse Effects of Aromatherapy:** The substances used in aromatherapy do not only have positive effects; as essential oils and fragrances can be sources of potential allergens, experts gathered at the international organization IFRA (International Fragrance Association) defined which essential oils and which components of them represent a potential allergy risk<sup>(15)</sup>.



**Figure 2. Mechanism of action of aromatherapy**

There are some, In general, synthetic fragrances contain irritants such as solvents and propellants, which can cause irritation in some people<sup>(37-39)</sup>. According to some studies, aromatherapy using pure aromas is safe. Aromatic oils used for the therapy have been shown to have very low toxicity profiles and to be safer than conventional pharmacological medications when administered by qualified practitioners<sup>(9)</sup>. However, it can be toxic at high concentrations, causing allergic reactions, photosensitivity, drug interactions, and carcinogenicity, particularly when taken orally<sup>(40,41,42)</sup>. According to a review of published case reports and case series, aromatherapy has the potential to cause adverse effects, some of which are serious, and that the frequency of such effects is unknown<sup>(43)</sup>. (The figure depicts the history of aromatherapy in different countries. It was first commenced by the Greeks in 500 BC followed by India in 2000 BC, China in 3000 BC and Egypt in 4500 BC.)



**Figure 3. History of aromatherapy**

**Link between Dementia and AD:** Dementia is a progressive brain disease that can impair memory, thinking, orientation, language, and judgment. Although decline in explicit memory is a prominent symptom of dementia, there is evidence that implicit memory can be preserved in patients with the disease<sup>(44)</sup>. In contrast, Alzheimer's disease (AD) is a progressive neurodegenerative disease that causes cognitive and noncognitive dysfunction. Despite the fact that a number of Alzheimer's drugs have been approved, they can only temporarily delay symptom progression, and no drugs can currently cure the disease. According to WHO.

The leading cause of dementia is Alzheimer's disease, accounting for 54% of all cases<sup>(45)</sup>, and it is expected to affect more than 115 million people worldwide by 2050<sup>(44)</sup>. The Amyloid hypothesis is a theory that describes the role of amyloid in the pathogenesis of Alzheimer's disease. As previously stated, amyloid beta peptide overturning is responsible for nerve cell toxicity or neurodegeneration. As a result, by inhibiting amyloid beta plaques, we can improve the condition of people suffering from Alzheimer's disease<sup>(46)</sup>. Atypical antipsychotics (Risperidone, Olanzapine, Aripiprazole, and Quetiapine) are used in the short term (6–12 weeks) for the pharmacological treatment of behavioural and psychological symptoms in dementia (BPSD). They tend to have limited efficacy and have been linked to serious side effects<sup>(47)</sup>. Thusim the drugs are used in combination with other nonpharmacological interventions. Aromatherapy, among alternative nonpharmacological treatments, has brought substantial evidence for agitation management in AD. Because of its tranquil nature, the essential oil used in aromatherapy aids in the induction of sleep and relaxation, as well as pain relief and the reduction of depressive symptoms<sup>(48)</sup>.

**Link between Olfactory sense and Dementia:** Previous research has found that olfactory impairment is frequently associated with Alzheimer's disease, and that more severe Alzheimer's disease is associated with the loss of additional olfactory abilities<sup>(49)</sup>. As a result, because essential oils are absorbed via transdermal administration or inhalation, their ability to be absorbed may be compromised. Similarly, the study conducted by Snow, Hovanec, and Brandt study has found no support for using a purely olfactory form of aromatherapy to reduce agitation in dementia patients because olfactory impairment may diminish the benefits of aromatherapy. However, most patients with Alzheimer's disease are not completely anosmic, and this varies depending on the type of dementia<sup>(50)</sup>. It's possible that even people with severe olfactory impairment can be able to achieve benefits of the treatment from smelling calming essential oils.

## CONCLUSION

Aromatherapy is the practise of promoting relaxation through the use of essential oils and helps to relieve stress. People has been using this method for decades. Although there is much case based evidence suggesting its positive effect in improving sleep, agitated behaviours and resistant to care in dementia, The mechanism of action of aromatic plant constituents has yet to be discovered. Additional basic research effort is necessary to understand the pharmacological mechanisms underlying aromatherapy, before conclusions can be drawn.

## REFERENCES

1. Wilson, RS., Arnold, SE., Schneider, JA., Boyle, PA., Buchman, AS., Bennett, DA. 2009. Olfactory impairment in presymptomatic Alzheimer's disease. *Ann N Y Acad Sci.*, 1170:730–735.
2. Nordin, S., Murphy, C. Impaired sensory and cognitive olfactory function in questionable Alzheimer's disease. 1996. *Neuropsychology.*, 10:113–119.
3. Maher, SM., Anderson, JK., et al. 1998. Development of an aromatherapy service at a cancer centre. *Palliat. Med.*, 12:171–180.
4. Esposito, ER., Bystrek, MV., Klein, JS. 2014. An elective

- course in aromatherapy science. *Am J Pharm Educ.*, 78(4): 79.
5. Ballard,CG., Gauthier, JS., Cummings, L., et al. 2009. Management of agitation and aggression associated with alzheimer disease. *Nat. Rev. Neurol.*,5:245–255.
  6. Ballard,CG., O'Brien, JT.,Reichelt, K., Perry, EK. 2002. Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a doubleblind, placebo-controlled trial with Melissa. *JClin Psychiatry.*, 63(7):553–558.
  7. Holmes, C., Hopkins, V., Hensford, C., MacLaughlin, V., Wilkinson, D., Rosenvinge, H. 2002. Lavender oil as a treatment for agitated behaviour in severe dementia: a placebo controlled study. *Int. J. Geriatr. Psychiatry.*, 17(4):305–308.
  8. Burns, A., Byrne, J., Ballard, C., Holmes, C. 2002. Sensory stimulation in dementia.*BMJ.*,325:1312–1313.
  9. Thompson, MD., Knee, K., Golden, CJ. 1998. Olfaction in persons with Alzheimer's disease. *Neuropsychol Rev.*, 8:11–13.
  10. Ou,MC., Hsu, TF., Lai, AC., Lin, YT., Lin, CC. 2012. Pain relief assessment by aromatic essential oil massage on outpatients with primary dysmenorrhea: a randomized, double-blind clinical trial. *J. Obstet. Gynaecol. Res.*, 38(5):817–822.
  11. Kia, PY., Safajou, FM., Shahnazi, M., Nazemiyeh, H. 2014. The effect of lemon inhalation aromatherapy on nausea and vomiting of pregnancy: A double-blinded, randomized, controlled clinical trial. *Iran. Red Crescent Med. J.*, 16(3).
  12. Watanabe, E., Kuchta, K., Kimura, M.,Rauwald, HWL., Kamei, T., Imanishi, J.2015. Effects of bergamot (*Citrusbergamia* (Risso) Wright &Arn.) essential oil aromatherapy on mood states, parasympathetic nervous system activity, and salivary cortisol levels in 41 healthy females. *Forsch Komplenmed.*, 22(1):43–49.
  13. Ali, B., Al-Wabel, NA., Shams, S.,Ahamad, A.,Khan,SA., Anwar, F.2015. Essential oils used in aromatherapy: a systemic review. *Asian Pac. J. Trop. Biomed.*, 5(8): 601–611.
  14. Dunning, T. 2013. Aromatherapy: overview, safety and quality issues. *OA Altern Med.*, 1(1): 6.
  15. Available online: <http://www.ifraorg.org> (accessed on 14 October 2017)
  16. Yildirim, Y., Parlar, S., Eyigor, S., Serto,OO.,Eyigor, C., Fadiloglu, C., et al. 2010. An analysis of nursing and medical students' attitudes towards and knowledge of complementary and alternative medicine (CAM). *J ClinNurs.*, 19(7–8):1157–1166.
  17. Huang,EJ.,Reichardt, LF. 2001. Neurotrophins: roles in neuronal development and function. *Annu. Rev. Neurosci.*, 24: 677–736.
  18. Michiaki,Okuda., Yuki, Fujita., Yuki, Takada-Takatori., Hachiro, Sugimoto., Katsuya, Urakami. Aromatherapy improves cognitive dysfunction in senescence-accelerated mouse prone 8 by reducing the level of amyloid beta and tau phosphorylation. *PLOS ONE.* 2020; 15(10).
  19. Bakhtshirin, F.,Abedi, S.,Yusefi,ZP.,Razmjooee, D. 2015. The effect of aromatherapy massage with lavender oil on severity of primary dysmenorrhea in Arsanjan students. *Iran. J. Nurs. Midwifery.*,20:156–160.
  20. Nikjou, R., Kazemzadeh, R., Rostamnegad, M., Moshfegi, S., Karimollahi, M., Salehi, H. 2016. The effect of lavender aromatherapy on the pain severity of primary dysmenorrhea: A triple-blind randomized clinical trial. *Ann. Med. Health Sci. Res.*, 6:211–215.
  21. Sayorwan, W. 2012. The effects of lavender oil inhalation on emotional states, autonomic nervous system, and brain electrical activity. *J Med Assoc Thai.*, 95:598-606.
  22. Schuwald, AM., Noldner, M., Wilmes, T., et al. Lavender oil-potent anxiolytic properties via modulating voltage dependent calcium channels. *PLoS One.* 2013;8.
  23. Ammar, A.H.,Bouajila, J.,Lebrihi, A., Mathieu, F.,Romdhane, M.,Zagrouba, F. 2012. Chemical composition and in vitro antimicrobial and antioxidant activities of Citrus aurantium L. flowers essential oil (neroli oil). *Pak. J. Biol. Sci.*, 21:1034–1040.
  24. Available online: <https://nhroorganiccoils.com/uploads/Allegens%20essential%20oils.pdf> (accessed on 19 August 2021).
  25. WHO Monographs on Selected Medicinal Plants. Available online: <http://apps.who.int/medicinedocs/en/d/Js4927e/> (accessed on 20 August 2021).
  26. Sugiura, T., Uchida, S.,Namiki, N. 2012. Taste-masking effect of physical and organoleptic methods on peppermint-scented orally disintegrating tablet of famotidine based on suspension spray-coating method. *Chem. Pharm. Bull.*, 60:315–319.
  27. Panahi, Y.,Taghizadeh, M.,Marzony, ET.,Sahebkar, A. 2015. Rosemary oil vs Minoxidil 2% for the treatment of androgenetic alopecia: A randomized comparative trial. *Skinmed.*, 13:15–21.
  28. Zarei, A.,Changizi AS.,Taheri, S., Rasekh, F. 2014. Comparison between effects of different doses of Melissa officinalis and atorvastatin on the activity of liver enzymes in hypercholesterolemia rats. *Avicenna J.Phytomed.*, 4(1):15–23.
  29. Guginski, G., Luiz, AP., Silva, MD., et al. 2009. Mechanisms involved in the antinociception caused by ethanolic extract obtained from the leaves of Melissa officinalis (lemon balm) in mice.*Pharmacol.Biochem. Behav.*, 93(1):10–16.
  30. Svoboda,KP., Deans, SG. 1995. Biological activities of essential oils from selected aromatic plants. *Acta Hort.*, 390:203-209.
  31. Svoboda, K., Hampson, J., Hunter, EA. Production and bioactivity of essential oils in secretory tissues of higher plants. In: *Proceedings of World Aromatherapy II Conference of National Association for Holistic Aromatherapy (NAHA)*; 1998 Sep 25–28; St. Louis, Missouri, USA; 105-127.
  32. Cook, N., Lynch, J. 2008. Aromatherapy: reviewing evidence for its mechanisms of action and CNS effects. *Br J NeurosciNurs.*, 4:595–601.
  33. de-Zambotti, M., Covassin, N., Sarlo, M., De-Min,TGD.,Trinder, J., Stegagno, L. 2013. Nighttime cardiac sympathetic hyper-activation in young primary insomniacs. *ClinAuton Res.*, 23:49–56.
  34. Patel,MB., McKenna, JW., Alvarez, JM., Sugiura, A., Jenkins, JM., Guillaumondegui, OD., et al. 2012. Decreasing adrenergic or sympathetic hyperactivity after severe traumatic brain injury using propranolol and clonidine (DASH after TBI study): study protocol for a randomized controlled trial. *Trials.*,13:177–186.
  35. Peters, JM., Hummel, T., Kratzsch, T., Lotsch, J., Skarke, C., Frolich, L. 2003. Olfactory function in mild cognitive impairment and Alzheimer's disease: An investigation using psychophysical and electrophysiological techniques. *Am J Psychiatry.*, 160:1995–2002.
  36. Eriksson, PS., Perfilieva, E., Bjork-Eriksson T., et al. 1998.

- Neurogenesis in the adult human hippocampus. *Nat Med.*, 4:1313–1317.
37. Silva-Neto, RP., Peres, MF., Valença, MM. 2014. Odorant substances that trigger headaches in migraine patients. *Cephalalgia.*, 34:14- 21.
  38. Vethanayagam, D., Vliagoftis, H., Mah, D., Beach, J., Smith, L., Moqbel, R. 2013. Fragrance materials in asthma: a pilot study using a surrogate aerosol product. *J Asthma.*, 50:975-982.
  39. Celeiro, M., Guerra, E., Lamas, JP., Lores, M., Garcia-Jares, C., Llompert, M. 2014. Development of a multianalyte method based on micro-matrix-solid-phase dispersion for the analysis of fragrance allergens and preservatives in personal care products. *J Chromatogr A.*, 1344:1-14.
  40. Lis-Balchin, M. The safety issue in aromatherapy (in:) *Aromatherapy science: A guide for healthcare professionals.* Pharmaceutical Press; 2005.
  41. Cook, A., Burkhardt, A. 2004. Aromatherapy for self-care and wellness. *Altern Complement Ther.*, 10(3):151-155.
  42. Bleasel, N., Tate, B., Rademaker, M. 2002. Allergic contact dermatitis following exposure to essential oils. *Australas J Dermatol.*, 43:211-213.
  43. Posadzki, P., Alotaibi, A., Ernst, E. 2012. Adverse effects of aromatherapy: A systematic review of case reports and case series. *Int. J. Risk Saf. Med.*, 24(3):147-161.
  44. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised (DSM-III-R)*, American Psychiatric Association, Washington, DC, USA, 1987.
  45. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders, (DSM-IV)*, American Psychiatric Association, Washington, DC, USA, 4th edition, 1994.
  46. Fleischman, DA., Wilson, RS., Gabrieli, JD., Schneider, JA., Bienias, JL., Bennett, DA. 2005. Implicit memory and Alzheimer's disease neuropathy. *Brain.*, 128:2006-2015.
  47. Barage, SH., Sonawane, KD. 2015. Amyloid cascade hypothesis: pathogenesis and therapeutic strategies in Alzheimer's disease. *Neuropeptides.*, 52:1–18.
  48. World Health Organization and Alzheimer's Disease International, *Dementia: A Public Health Priority*, World Health Organization, Geneva, Switzerland, 2012.
  49. Hardy, JA., Higgins, GA. 1992. Alzheimer's disease: the amyloid cascade hypothesis. *Science.*, 256:184–185.
  50. Ballard, C., Corbett, A. 2013. Agitation and aggression in people with Alzheimer's disease. *Curr Opin Psychiatry.*, 26(3):252–259.

\*\*\*\*\*