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### Abstract

The importance of aromatherapy in alternative or complementary medicine and the history of its application in mood enhancement is briefly reviewed. The sense of smell or olfaction, central to the identification of odors and to aromatherapy is discussed in some detail. The characteristics and psychological problems associated with anxiety are reviewed before the application of aromatherapy in anxiety-management is discussed. Finally, the neurological basis for the anxiolytic efficacy of aromatherapy is re-evaluated.

Keywords: Aromatherapy; Complementary Medicine (CAM); Mood-Elevation

# Introduction

Aromatherapy is that form of alternative or complementary medicine (CAM) which uses essential oils to enhance physical and psychological well-being. These essential oils are the natural oils extracted from flowers, bark, stems, leaves, roots or other parts of a variety of plants. The underlying basis for aromatherapy is that the inhaled aroma from these essential oils is believed to stimulate brain function. Essential oils can also be absorbed through the skin such that the bloodstream facilitates their distribution throughout the body, thereby promoting whole-body healing. This latter application of essential oils is known as massage therapy.

Aromatherapy has been in active use for thousands of years and now, in the 21<sup>st</sup> Century, it is increasingly used for a variety of applications, including pain relief, mood enhancement and increased cognitive function. Healthcare professionals, patients and general users find that aromatherapy enhances the quality of life (QOL) by improving their psychological, spiritual and physical well-being. Anecdotal, apocryphal and now clinical studies indicate that aromatherapy is useful in directly treating and functioning as an adjunct therapy for an array of symptoms and conditions. It is effective in mood enhancement and elevation, notably for stress relief and to offset anxiety and depression as well as to limit pain. It is also used to improve cognitive function, notably thinking, reasoning, memory and imagining. Most scientific studies of aromatherapy have been directed at its psychological effects, notably stress relief and reducing anxiety.

With regard to the term aromatherapy, it should be mentioned, however, that such noted advocates of the antibacterial activity of essential oils, namely Gattefossé and Valnet, referred to this medicinal use of essential oils as "aromatherapie" (the French word for aromatherapy). Other workers have used a similar nomenclature in reporting their research studies with essential oils but, in the present context, the term aromatherapy refers only to the effects of inhalation of essential oils.

Before discussing the effectiveness of aromatherapy in treating anxiety, it might be useful to briefly review the sense of smell and the nature of anxiety.

#### The sense of smell

Few people are immune to the effect of aromas and pleasant smells. Most delight in smelling a rose and even people who don't drink coffee will admit to liking the aroma of fresh-ground coffee beans. Aromas have an evocative, almost subliminal effect on the mind, and the conjuring up of memories by different smells is very common and is referred to as the Proust effect [1]. This effect refers to the reliving of events from the past through sensory stimuli that evoke an intense and emotional memory of an episode from, typically, one's childhood although, compared to the science of memory deficits, little is actually known about the physical and sensory pleasures of remembering.

The sense of smell or olfaction<sup>1</sup> is the unique sense by which odorants are perceived [2,3]. Despite the fact that olfaction monitors the intake of airborne agents into the human respiratory system and determines to a large degree the flavor and palatability of foods and beverages, it is an underappreciated sense [4]. Not only does the sense of smell enhance the quality of life, but it is also the primary sensory warning system against spoiled foods, leaking gas, noxious chemicals, polluted air and smoke as well as mediating basic elements of communication (e.g. mother-infant interactions) [4].

Olfaction is the complex neurological response to the nasal inhalation of an odorant [5] and has many functions, including detecting and identifying desirable (and undesirable) foods, hazards and pheromones as well as influencing taste. It involves the binding of the odorant to a receptor or multiple receptors within the nasal cavity, the receptor then transmitting a signal through the olfactory system to the brain [6].

The olfactory system is likely one of the oldest sensory systems but in many ways may be the least understood of the sensory modalities. The olfactory system processes information about the identity, quality and concentration of a wide range of chemical stimuli, i.e. odorants. The latter, when inhaled, interact with olfactory receptor neurons in an epithelial sheet lining the interior of the nose. The axons arising from these receptor cells project or communicate directly to neurons in the olfactory bulb, the latter in turn projecting or transmitting signals to the pyriform cortex in the temporal lobe. The olfactory tract also transmits signals to other forebrain targets, including the hypothalamus and amygdala. Signals from the pyriform cortex and other forebrain regions provide olfactory information via the thalamus to several additional regions of the cerebral cortex. The further processing that occurs in these other regions of the brain identifies the odorant and initiates appropriate motor, visceral and emotional reactions to olfactory stimuli.

As indicated above, the brain's olfactory bulb is where the sensory input starts to interact with those parts of the brain responsible for neural responses to odorants. This process involves glomeruli, small spherical structures located near the surface of the olfactory bulb and which are the location of synapses formed between the terminals of the olfactory nerve and the dendrites of a variety of cells. In fact, each glomerulus is surrounded by a heterogeneous population of neurons of juxtaglomerular or granular cells. Glomeruli typically range between 50 - 120 µm in diameter and there are roughly 1100 and 1200 in humans [7]. However, the number of glomeruli in humans decreases with age such that there is major impairment in olfaction for people over 80 years in age [8]. This trend accounts for the reduced olfaction sensitivity in older people.

Glomeruli are the initial sites for synaptic processing or nerve transmission of odor information coming from the nose and, basically, are critical for odorant signal transduction or signaling. Each glomerulus receives input from olfactory receptor neurons expressing only

<sup>&</sup>lt;sup>1</sup>The medical term for the sense of smell or olfaction is osmesis.

one type of olfactory receptor and the glomerular activation patterns within the olfactory bulb apparently represent the quality of the odor being detected. However, these glomeruli activation patterns can change due to alterations in airflow rate and odor concentration in the mucus layer of the nasal cavity and a particular odorant can activate a glomerulus strongly whilst affecting others with less efficiency or not at all. Thus, it appears that each odor activates a different pattern of glomeruli, such that the olfactory bulb, and hence the brain, can perceive the odor.

It follows from this that olfaction is a complex process. In basic terms, after inhalation of an odorant, glomeruli aggregate signals from olfactory receptor neurons in the nose and then transmit them to the olfactory bulb. Thereafter, the sensory input will start to interact with those parts of the brain responsible for smell perception, memory and emotion [9].

The loss of the sense of smell can be partial (hyposmia) or complete (anosmia), and depending on the cause, may be temporary or permanent. Congenital anosmia (inability to smell or lacking a sense of smell from birth) is uncommon although some people may be anosmic or unable to smell a particular odor or aroma, a condition known as specific anosmia. Likewise, hyposmia or a decreased ability to smell anything is not uncommon, particularly when suffering from a cold, influenza or blocked sinuses.

There are many causes for a change, absence or disturbance of a normal sense of smell, and these can include damage to the nose or smell receptors, or neurological problems affecting the brain. Other causes include upper respiratory infections, traumatic brain injury and neurodegenerative disease. In fact, olfactory dysfunction is one of the earliest nonmotor features of neurodegenerative diseases such as Alzheimer's disease (AD) and sporadic Parkinson's disease (PD) [10,11]. Such dysfunction is not understood but occurs in approximately 90% of early-stage PD cases and can precede the onset of motor symptoms by several years [11].

#### Anxiety

Anxiety is a common and unpleasant emotion of inner nervousness that is a normal response to both perceived and actual danger as well as to stress. Interestingly, despite being a recognized and debilitating problem for thousands of years, anxiety disorders were only classified as a mental illness in the 20<sup>th</sup> Century [12].

Anxiety disorders is the nonspecific term for a wide range of mental disorders that include generalized anxiety, panic, a variety of phobias, post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) [10,13]. In fact, anxiety disorders are the most common mental illness in the United States (and probably globally), with the 12-month prevalence affecting about 10% of the adult population, i.e. about 6.8 million adults [13-17]. Afflicted individuals typically exhibit both psychiatric and somatic symptoms, with the occurrence of generalized anxiety disorder (GAD) in women being twice that in men, with the disorder often starting during adolescence. The common manifestations of general anxiety disorder are indicated in table 1.

When a person is anxious, the brain releases neurotransmitters, typically dopamine, serotonin, epinephrine, acetylcholine and histamine. It should be noted in this context that low levels of serotonin can give rise to the symptoms of depression and anxiety. However, consuming foods such as dairy products and nuts (i.e., so-called mood foods) that are rich in tryptophan, which acts as a precursor of several neurotransmitters including serotonin, will raise serotonin levels and reduce anxiety. These neurotransmitters released by the brain put the body into a high state of alert, preparing the body for the "fight or flight" response to a perceived threat. However, some of the neurotransmitters can and will enter the digestive tract and disrupt the gut microbiome and can result in nausea. As a result, gastric problems such as nausea and diarrhea are common symptoms of stress and anxiety, and ingress of neurotransmitters into the gut, and their effect on the microbiome, is a common cause of peptic ulcer disease.

Nausea, indigestion and diarrhea Stomach cramps Loss of appetite or unnatural hunger Irritable bowel syndrome (IBS) Peptic ulcers Constant feelings of worry and tension Excessive concern over simple, everyday tasks Feeling of constantly being "on edge" or easily startled Irritability and mood swings Inability to relax Lightheadedness or shortness of breath Restlessness Unrealistic view of problems Difficulty in concentrating Perpetual tiredness Difficulty falling asleep or staying asleep **Frequent headaches** Depression symptoms Muscle tension, aches and body pains Trembling or twitching Difficulty in swallowing Sweating Frequent urges to urinate and/or have a bowel movement Panic attacks Intense separation anxiety Alcohol and substance abuse

Table 1: Anxiety disorder symptoms.

Unfortunately, a great many mental health patients face problems in receiving proper treatment. This treatment gap has led to a global mental health crisis, with up to 90% of people with mental health problems in some countries being unable to receive even basic treatment [18]. For example, a survey for the years 2001 - 2005 showed that only 8% of the people with mental illness in China sought professional help and only 5% of them had received psychiatric treatments [19]. Comparable situations with regard to mental health and its treatment are likely a global problem.

#### Conventional approaches to mood-elevation and anxiety relief

There is a long history of relieving stress, tension and anxiety using drugs, with alcohol being considered to be the earliest treatment [12,20]. The main treatments for anxiety disorders prior to the 20<sup>th</sup> Century were sedative and hypnotic drugs such as bromides and chloral hydrate and, in the early to the middle years of the 20<sup>th</sup> Century, barbiturates were commonly used as anxiety treatments [12]. Unfortunately, barbiturates have severe addictive and other side-effects, and were replaced in the 1950s by benzodiazepines (BDZs) which

act on γ-aminobutyric acid (GABA) receptors [21]. Problems such as excessive sedation, headaches and withdrawal symptoms were found with BDZs in clinical practice [12]. This led to the development of drugs based on 5-hydroxytryptamine (5-HT), neuropeptide, glutamate and endocannabinoid systems and, notably, buspirone and the selective serotonin reuptake inhibitor (SSRI), fluoxetine [22,23]. Nevertheless, despite the advances made in chemotherapeutics, anxiety sufferers still may experience severe adverse reactions and dependence while many find such drugs ineffective.

This situation has resulted in a re-awakening of interest in CAMs and, in particular, there has been a resurgence of attention being paid to traditional and folk medicine in many countries. This interest is based on the growing awareness that traditional medicinal practices rely on the mood-elevating and insomnia-alleviating effects in addition to the analgesic, antibacterial, anti-inflammatory activity of essential oils [13,24-27].

#### Aromatherapy, mood enhancement and anxiety

Until quite recently, most of the reported anxiolytic and relaxational effects associated with essential oils have been anecdotal but this situation has now changed. One development is the wide availability of efficient and reasonably-priced nebulizers/diffusers for vaporization of essential oils dispersed in water. Another major development has been the increasing numbers of scientific and clinical studies on essential oils and aromatherapy reported in the literature every year. One result of this increased scientific interest and scrutiny is that aromatherapy is recognized as an effective and beneficial complementary therapy for people with anxiety symptoms.

Several years ago, there was a review of 16 randomized controlled clinical trials reported in the literature from 1990 to 2010 on the use of aromatherapy for people suffering from anxiety or exhibiting anxiety symptoms. Most of the reviewed studies indicated positive effects in controlling anxiety with aromatherapy and an absence of adverse events being reported [28].

Many essential oils are believed to be effective anxiolytic (anxiety-reducing) agents, table 2, resulting from their aromas have a calming, relaxing and soothing effect on the mind and body [24,29-32].

Bergamot
Chamomile
Frankincense
Geranium
Lavender
Lemon
Pine
Rose
Rosemary
Salvia
Sandalwood
Sweet Orange
Ylang-ylang

Table 2: Anxiolytic (anxiety-reducing) essential oils.

A great many research reports have been centered on lavender oil aromatherapy for a number of different clinical applications [24,33-40]. Further, there has been a growing trend for medical and dental offices to place aromatherapy diffusers containing lavender oil within waiting rooms to help alleviate patient anxiety. This evidence-based validation of the safety and effectiveness of aromatherapy is of growing importance given the limitations and risks associated with existing pharmacotherapies for treating anxiety disorders. There remains, however, the open question of how aromatherapy exerts its anxiolytic effects.

A clinical study was performed several years ago that involved 200 dental patients in the age range of 18 - 77 y.o, 50% male and 50% female and investigated the impact of aromatherapy on anxiety, mood, alertness, and calmness [41]. The test subjects were divided into 4 independent groups: 1) Control group; no odor, no music; 2) Music group (no odor), 3) orange aroma, and 4) lavender aroma. It was found that anxiety was reduced and mood was improved with orange and lavender aromas compared to controls but there was no effect due to music. No significant differences in alertness were noted between control and all groups although calmness was improved slightly with orange aroma and significantly with lavender aroma. Overall, music appeared to have no effect on patients.

Despite the success for this study and those reported with other clinical studies, questions have been raised regarding the efficacy of aromatherapy in that the treatment regimen could be an effective placebo rather than an effective anxiolytic agent [22,42,43]. On the other hand, a very recent study [44] described a randomized, double-blinded and placebo-controlled study to evaluate the effectiveness of an aroma therapy regimen on women who had recovered from COVID-19 but reported experiencing fatigue. In this report, both the control and intervention groups inhaled either an essential oil blend or fractionated coconut oil (placebo) twice daily for a total of 30 minutes for 14 days. The reported outcomes were that the intervention group had statistically significant improvements in vigor and energy as well as significant reductions in both mental and physical fatigue. This finding that aromatherapy using a proprietary essential oil blend effected improvement in energy levels among women who are experiencing fatigue after recovering from COVID-19 is quite remarkable and is a clear and scientifically validated indication that aromatherapy with the appropriate essential oils can address many of the anxiety symptoms indicated in table 1.

Finally, it has also been reported that exposure to essential oil emissions reduced reaction time but significantly impacted inhabitation control and memory sensitivity, indicating potentially more impulsive decision-making [45]. It has also been reported recently that ultrasonic essential oil diffusers emit large quantities of volatile organic compounds (VOCs) and particulate matter, with the type of essential oil determining the amount and size distribution of emitted particulate matter and the amount and VOC fingerprint [46]. Interestingly, using tap, rather than distilled, water in an ultrasonic diffuser is reported to result in much higher emissions of particulate matter [44].

#### The scientific basis of aromatherapy

Despite the research efforts expended on olfaction, aromatherapy and the treatment of mental illnesses such as anxiety, how aromatherapy exerts its anxiolytic effects is not fully elucidated. Aromatherapy and olfaction both involve odorants stimulating smell receptors in the nose, which then send messages through the nervous system to the limbic system, that part of the brain controlling emotions. As discussed previously, in the olfactory system, chemical components of essential oils activate olfactory receptors and when the signals are transferred to the olfactory bulb and the brain, gamma aminobutyric acid (GABA) receptors and transient receptor potential channels (TRP) mostly play a role [47]. It should also be noted that synergistic effects between the constituents of essential oils also affect the mechanisms of action of the essential oils [24,47].

Central to aromatherapy is that olfaction affects the limbic system of the brain, which is directly connected to those parts of the brain that control heart rate, blood pressure, breathing, memory, stress levels, and hormone balance. This is shown schematically in figure 1.

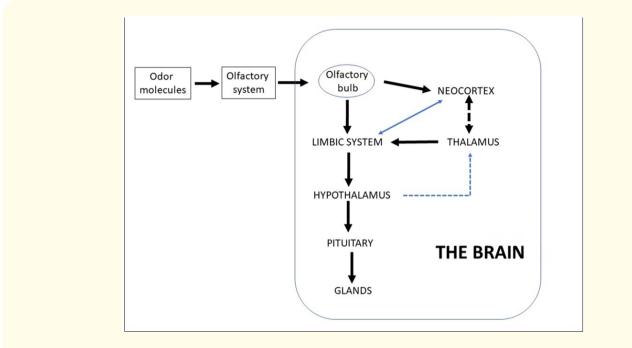


Figure 1: Schematic diagram of olfactory signal processing.

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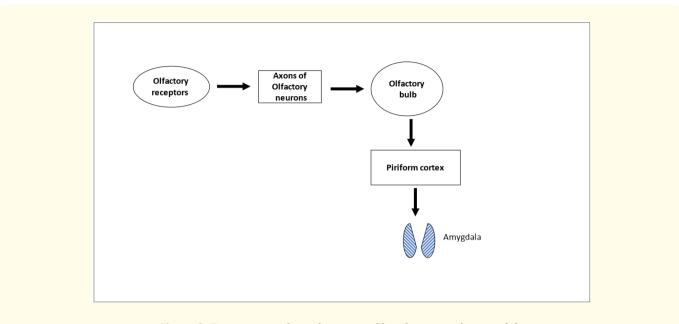
When an odorant, the ligand messenger, enters through the nasal passage, it stimulates the olfactory neurons by interacting with cell receptor sites. The latter are glomeruli located near the surface of the olfactory bulb and which are the location of synapses formed between the terminals of the olfactory nerve and the dendrites of a variety of cells. When the ligand messenger interacts with the appropriate and specific cell receptor, the receptor generates a signal that is transmitted to the olfactory bulb and then to the neocortex and to the limbic system in the brain. Thus, these receptors initiate subsequent events that trigger action potentials (minute electrical impulses) that are propagated up the olfactory nerve to the limbic system<sup>2</sup> in the brain, particularly the amygdala<sup>3</sup>. The amygdala gland in the brain is where trauma and negative emotions are stored and only the sense of smell or olfaction can cause this gland to release the trauma and stored negative emotions. This pathway is indicated in figure 2.

The limbic system [48] releases neurochemicals that are transmitted to the hypothalamus which, in turn, sends these chemicals to the pituitary gland and then on to the different systems in the body. In fact, the hypothalamus is one of the most important parts of the brain since it is the "hormonal control center", releasing chemical messengers that can affect everything from sex drive to energy levels.

<sup>2</sup>The limbic system is a system of nerves and networks in the brain, involving several areas near the edge of the cortex. It controls the basic emotions (e.g. fear, pleasure and anger) and human drives (e.g. hunger, sex, dominance and care of offspring).

<sup>3</sup>The amygdala is one of two almond-shaped groups of nuclei located deep within the temporal lobes of the brain and is the integrative center for emotions and motivation. The amygdala gives rise to fear when facing things outside personal control, notably the reaction to certain stimuli or an event that is seen as potentially threatening or dangerous.

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Figure 2: Transmission of signals generated by odorants to the amygdala.

In addition, there is an exchange signaling system between the neocortex and the thalamus as well as a signaling feedback loop between the hypothalamus and the thalamus. These additional exchanges and interactions stimulate and improve the efficacy of the neurotransmission effects within the limbic system. Since this is the same part of the brain that controls emotion, odorants can cause direct stimulation of the emotional center in the brain. These feedback pathways are indicated in figure 1.

Other research studies indicate that aromatherapy with essential oils is related to decreased levels of cortisol<sup>4</sup>, reduced inflammation, lowered heart rate, reduced anxiety and alleviates depression [49,50].

It should be noted, however, that many factors will influence the effectiveness of aromatherapy, notwithstanding the fact that a strong Hawthorne effect<sup>5</sup> may also be occurring.

It follows from the above discussion of aromatherapy that the inhalation of essential oils can be used to combat stress and trauma, but it can also stimulate the production of hormones from the hypothalamus.

<sup>5</sup>The Hawthorne effect refers to the way participants may alter their behavior as a result of being part of an experiment or study; in other words, because trial participants can smell an essential oil, they might expect a positive effect regardless of whether that effect actually occurs.

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<sup>&</sup>lt;sup>4</sup>Cortisol is the hormone released by the adrenal gland in response to stress and low blood glucose; its actions include increasing blood sugar, suppressing the immune system and aiding in the metabolization of protein, fat and carbohydrates.

# Conclusion

The anxiolytic activity elicited by aromatherapy is likely the result of both mood enhancement and physiological changes, with the mood-based changes also possibly depending on subjective memories that are tied to particular scents. These effects arise from the interaction of odorants with the limbic system which plays a pivotal role in behavior, especially through the hormonal releases of the hypothalamus and amygdala.

Thus, not only can the inhalation of essential oils be used to reduce fatigue, combat stress and trauma, but it can also stimulate the production of hormones from the hypothalamus. It is also well-established that fear and rage responses are produced by the stimulation of the hypothalamus and amygdala. Apparently, aromatherapy has the effect of quietening or reducing situational stimulation of the hypothalamus and amygdala, thereby inducing anxiolytic effects.

It is also apparent from numerous blogs and other literature that the type of essential oil may strongly influence the perceived benefits of the aromatherapy regimen. Even the water used in the ultrasonic diffuser can significantly affect the volatile emissions. Nevertheless, despite some reservations in the literature regarding the effectiveness of aromatherapy as an anxiolytic therapy, the preponderance of the literature clearly indicates that this CAM modality is a valuable anxiety treatment.

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