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Review Article

Floral Aromas – The Fragrant Pathway to Exuberant Health concealed in the Mahamrityunjaya Mantra

Sharadendu Bali*

MS (General Surgery), PhD (Biochemistry); Professor General Surgery, TMMC, TMU, Moradabad, UP, India

***Corresponding Author:** Sharadendu Bali, MS (General Surgery), PhD (Biochemistry); Professor General Surgery, TMMC, TMU, Moradabad, UP, India.

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1. Abstract

The Mahamrityunjaya mantra is one of the oldest and most powerful mantras in Indian religious tradition, and is considered to have the ability to ward off untimely death. The mantra is quite short, consisting of 12 words, but each word is highly significant as regards the impact on health. The present article hinges around the significance of the three words " Sugandhim pushti vardhanam", that form part of the mantra. These words can be translated as : "Fragrance enhances well-being". It is already known that smells perceived by the brain are inextricably inter-twined with emotions and memory, and that odours can affect mental and physical health in several ways. It is also now being recognized that molecules of aromatic compounds and fragrances can easily reach the brain through the nose. In fact, the ancient Indian medical texts and seers have always considered the nose to be the "Gateway to the Brain".

Novel pharmaceutical formulations are being currently developed to deliver drug molecules to the brain through the nasal route. The recent discovery of brain lymphatics supports the view that fragrant substances can easily access the brain via the cribriform plate, along the filaments of the olfactory nerve. The brain being the master controlling organ of the body, influences all bodily functions. Thus, any aroma molecule, after entering the brain, can easily impact brain neurons, and thereby modulate other systemic functions, in part through the autonomic nervous system. Aroma compounds can also affect various body tissues through another mechanism involving extra-sensory olfactory (smell) receptors. These smell receptors are present on the cell membranes of tissues of several body organs, and can perceive and respond to the inhaled aroma compounds, reaching the tissues through the blood stream. It is hence apparent that pleasing aromas can positively affect human health, enhancing well-being and longevity.

Keywords: Mahamrityunjaya Mantra; Mantra for Health; Aromatherapy; Fragrance Benefits; Neurogenesis; Smells and Emotions

Abbreviations

EO: Essential Oil; EEG: Electroencephalography; PCI: Percutaneous Coronary Intervention; SWS: Slow-Wave Sleep; COPD: Chronic Obstructive Pulmonary Disease; NO: Nitric Oxide; CO: Carbon Monoxide; H2S: Hydrogen Sulfide; EOSF: EO of the Seed of Ferula Asafoetida; LPS: Lipo Polysaccharide; GSH: Glutathione; ROS: Reactive Oxygen Species; HFD: High-Fat Diet; OB: Olfactory Bulb; ORN: Olfactory Receptor Neuron; RMS: Rostral Migratory Stream; OR: Olfactory Receptor; MOA: Mechanism of Action

2. Introduction

The study of the influence of odors on human behavior, feelings and emotions is known asin Ind Aromachology. The impact of aromas is effectuated by the stimulation of the olfactory system, which further projects this effect through the limbic system of the brain. The limbic system comprises the Cingulate gyrus, Parahippocampal gyrus, Dentate gyrus, Hippocampus, Amygdala, Septal area and the Hypothalamus. These brain regions are responsible for modulating emotions and behavior. Though it is well known that fragrances affect human emotions, moods and behavior, the varied physiological effects on the different body systems are less well explored. Even more so, the effects of aromas on longevity, intellectual capacity and preventing diseases are less well known. The study of the beneficial effects of aromas on human health is popularly known as Aromatherapy.

In India, aromatherapy has been embedded in the culture of its people for millennia. Since ancient times, men and women in India have adorned garlands of scented flowers (called malas), such as jasmine and marigolds, around the neck and hair, and also as ornaments for wrists, affording a continual day long experience of aromatherapy. Specific flowers are offered to specific deities, and this tradition has been faithfully maintained over the centuries. On entering the premises of a temple, the aromas exuded by the flowers, incense sticks (agarbattis), fumes from diyas (oil lamps), camphor, and the prasad (food offering) provide a refreshing experience and enliven the spirit (Figure 1). It is interesting to note that ancient Indian aromatherapy does not limit itself only to inhaling fragrances, but also utilizes the fragrant herbs for local application. For instance, dried sandalwood and rose petals are ground into a paste with water, and applied on the body or on wounds. Incenses and fragrances are also used in many different ways in the Indian religious tradition.

In fact, the ancient Indian cultural, culinary and religious traditions are interwoven to such an extent that it is impossible to differentiate one from the other. Religious practices and rituals are in many instances related to particular types of foods, drinks, trees, flowers and perfumes. Music, chants and sounds are used in religious and cultural activities to a very great extent. The ancient Vedic texts are composed of Sanskrit verses, each spoken in a particular fashion. There are different verses for each and every occasion and ceremony, and these verses, calked shlokas, are pregnant with meaning. Different scholars can interpret the same mantra in many different ways. This paper is being written in this context, in an attempt to decipher the hidden significance of the following three words that form the second line in the short four-line Maha Mrityunjaya Mantra (MMM): "Sugandhim Pushti Vardhanam".

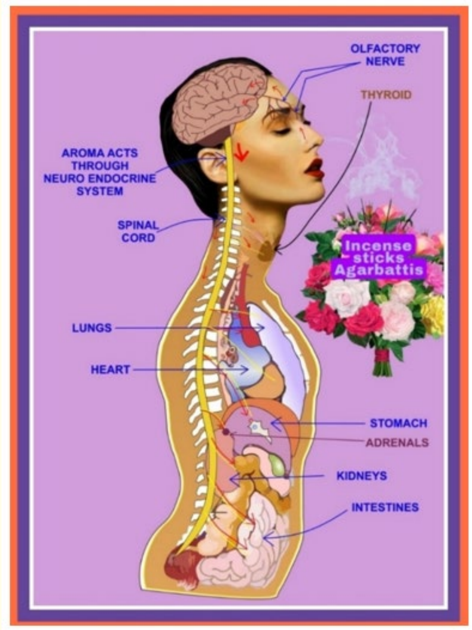

Figure 1: Agarbattis, or incense sticks, provide a convenient means to enjoy various delightful aromas. Aromas are sensed by the olfactory nerve, and exert actions on the brain and body systems via the spinal cord and neuro-endocrine axis.

Recent research studies have shown that fragrances can exert their actions by affecting vital brain regions, such as the hypothalamus and limbic system, through the neuronal connections that exist between these regions and the olfactory tract [1]. Fragrances trigger olfactory stimulation that can quickly affect brain activity, muscle tension, blood pressure, skin temperature, pupillary dilation, and pulse rate [2]. The EEG recording is a simple technique to evaluate the changes in brain function caused by fragrances. Fragrance compounds can also reach the brain directly through the cribriform plate located in the roof of the nasal cavity. There is now extensive evidence suggesting olfactory effects on mood, emotional state, behaviour, and physiology [3].

3. Aromatherapy – pleasant smells have health benefits

3A. Effects of aromatherapy on the brain

Extensive research has been carried out on aromatherapy and its effects on the brain and the neuroendocrine system. Bentley., *et al*. in 2023 examined the impact of smells of nature and woodland on human well-being through an experiment conducted in Sherwood Forest [4]. Study results demonstrated that specific smells **promote relaxation**, rejuvenation, and comfort. Some particular smells contribute to spiritual, emotional, cognitive, physical, or global well-being [5]. Smells that trigger reminiscence experiences can assist people with dementia to retain their sense of identity [6]. Additionally, such smells positively affect cognitive function and help cope with symptoms of depression [7]. It has also been demonstrated that some scents are associated with **improved well-being**, and smells in nature can help deal with a variety of mental health issues and illnesses [8]. Ko., *et al*. investigated the effects of inhaling lavender oil on sleep quality. Nine young men and women inhaled the scent of lavender essential oil over two nights. Electroencephalography (EEG) and sleep patterns were recorded before and after inhalation of the aroma oil. The findings indicated that olfactory stimulation with lavender aroma caused a reduction in alpha wave activity in wake stage, and an increase in delta waves, alongwith an increase in slow-wave sleep (SWS) [9]. These results suggest an **improvement in sleep quality** due to inhalation of lavender oil.

Cho., *et al*. in 2015 showed that inhaling the Magnolia kobus fragrance caused a decrease in the absolute alpha wave on EEG, which reflects **improved concentration and alertness** [10]. Such studies demonstrate that different scents with awakening and sedative effects can benefit mental focus, concentration, and clarity [11]. Olfactory environments can also play an important role in alleviating stress, enhancing self-esteem, and increasing overall happiness [12]. The fragrance of plum blossoms was found to **boost memory** and support emotional well-being [13]. Emotions and behavior are mostly modulated by the limbic system of the brain, which is in close proximity to the olfactory tract and pathways, and are hence directly affected by odors and smells (Figure 2). Jiang., *et al*. 2021, in their study found that aromatic stimulation by fragrant Primula flowers induced higher alpha values and attention scores [14]. Study results suggested that Primula fragrances **promote emotional stability**, comfort, relaxation, and attention, thus confirming a strong psychological and physiological impact. Rho., *et al*. (2007) studied the effects of massage with essential oils of lavender, chamomile, rosemary, and lemon in elderly Korean women [15]. They concluded that such perfumed massages may reduce anxiety levels and improve self-esteem. Kim., *et al.* demonstrated that aromatherapy massage using a blend of essential oils (rosemary, lemon, and peppermint) significantly alleviated constipation among the elderly subjects [16].

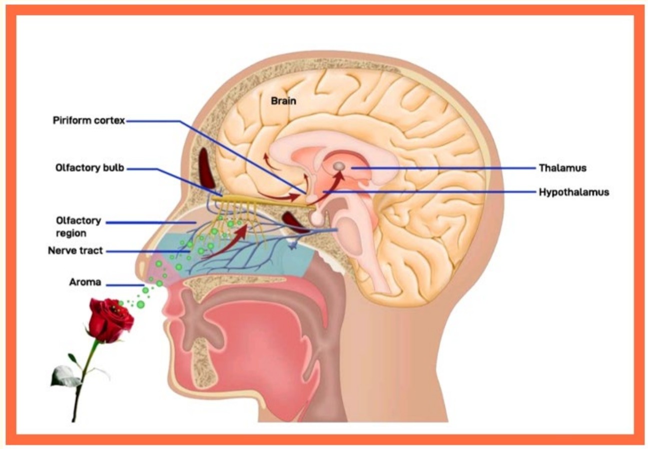

Figure 2: Aromas cause their effects by stimulation of the Olfactory nerve, as well as by direct entry of fragrance compounds into the brain through the cribriform plate. The olfactory tract lies in close proximity to the hypothalamus, piriform cortex, and other areas of the limbic system, allowing aromas to affect emotions and behaviour (see Section 5.3).

It has been demonstrated by Moss., *et al*. 2023, that exposure to particular aromas can help **improve cognitive function** [17]. Previously, in 2008 also, Moss led a study that sought to examine the effects of peppermint and ylang-ylang aromas on cognition and mood in healthy individuals [18]. A group of 144 volunteers was randomly allocated into three groups : exposure to peppermint aroma, ylang-ylang aroma, or no aroma (control). The study revealed that peppermint significantly boosted memory and alertness levels, while ylang-ylang showed stress reduction properties. Chamine and Oken conducted experiments in healthy subjects to evaluate the effects of lavender aroma on cognition and psychophysiological activity following stress, as compared to placebo aromas [19]. Study results showed that lavender aromatherapy **improved post-stress working memory** via key mechanisms involving aroma-specific pharmacological actions, hedonic properties, and participants' expectations. Lavender has also been proven to be an effective **pain reliever** due to its relaxing odor [20].

In 2013, Varney and Buckle found that inhaling a mixture of essential oils, including peppermint, had a positive impact on individuals suffering from **mental exhaustion or moderate burnout** [21]. The study participants reported reductions in perceived stress and improved mood following aromatherapy, demonstrating its potential in the workplace or high-stress environments. Toda and Morimoto (2011) observed that study participants exposed to peppermint aroma showed significant reductions in salivary cortisol levels. Since cortisol is a "stress hormone", findings of this study suggest that peppermint aroma could potentially be used as a tool for **stress relief** [22]. A study led by Moss., *et al*. (2023) showed that the presence of peppermint aroma in a simulated driving environment resulted in significant **reductions in aggressive driving** [17].

Neumann., *et al*. 2020 analysed the positive effects of odour cues in school children. The study found that presenting odour cues during learning and selectively during slow wave sleep increases learning [23]. Study results concluded that odour cues can significantly benefit mental well-being and **memory** via selective learning during sleep. Cho., *et al*. in 2013 evaluated the impact of aromatherapy with a blend of lavender, neroli, and roman chamomile in percutaneous coronary intervention (PCI) patients [24]. During the study, significant changes were observed in the anxiety level of patients treated with aromatherapy, exhibiting the **anxiety-decreasing** potential of aromatherapy. Aromatherapy has also been proven to enhance sleep quality and reduce anxiety in cancer patients [25]. One study showed that aromatherapy positively affected sleep satisfaction in night shift nurses [26].

Glass and Heuberger in 2016 assessed whether age plays a role in the magnitude of the effect of natural odours on **mood** [27]. A complex mixture containing a combination of smells including river water, plant fragrances, and barbecues aromas, was used as stimulus material. Study results showed that all age groups experience positive effects of fragrances, including improved mood, calmness, alertness, and better emotional state. Ke., *et al*. in 2022 investigated the benefits of aromatherapy on mental and physical health in aging individuals [28]. They concluded that aromatic essential oils help regulate the nervous system and emotions and reduce physical pain through olfactory stimulation. Study results demonstrated significant reduction in stress, and improved physical and mental health in middle-aged and elderly participants after aromatherapy intervention. Aromatherapy is widely used in Taiwan's elderly care institutions to help residents and cancer patients **reduce stress** and relax, as well as to enhance the physical and emotional health of individuals [29]. Further, a research study concluded that aromatherapy is beneficial in the treatment of cardiovascular diseases and depression, improving the quality of life in the elderly [30].

The volatile root oil of Angelica archangelica contains monoterpenes such as 3-carene, α-pinene, and limonene, which have demonstrated **anti-epileptic** activity in mice [31]. Similar anti seizure activity of essential oil of A. archangelica was observed in an earlier study conducted by Pathak., *et al*. in 2010 [32]. In mice models, inhalation of Lavandula angustifolia (English lavender) oil vapour 15 minutes before treatment with pentylenetetrazole prevented all convulsions in100% of the animals and prevented mortality. The active compound was found to be Linalool [33].

3B. Systemic Effects of aromas on various Physiological Functions (Figure 3)

Besides the positive effects of fragrances on the brain, the rest of the body is also favourably impacted. Sowndhararajan and Kim 2016 reviewed the direct and indirect physiological effects of fragrances on various organ systems and psychological conditions [34]. Their findings indicated that inhalation of lavender oil resulted in more active, fresher, and relaxed subjects than those inhaling base oil. Lavender oil increased the theta and alpha wave activities on EEG, when compared with base oil. In the athletic task performance test, they found that peppermint odour significantly increased running speed, hand grip strength, and number of push-ups, but had no effect on skill-related tasks [35]. In a study the following year, Raudenbush., *et al*.2002 studied the effects of peppermint and dimethyl sulfide administration on objective and subjective measures of physical performance of athletes [36]. They observed that peppermint aroma inhalation resulted in better performance and vigour, and lower effort and fatigue. Dimethyl sulfide odour usage enabled the athletes to endure higher physical workload.

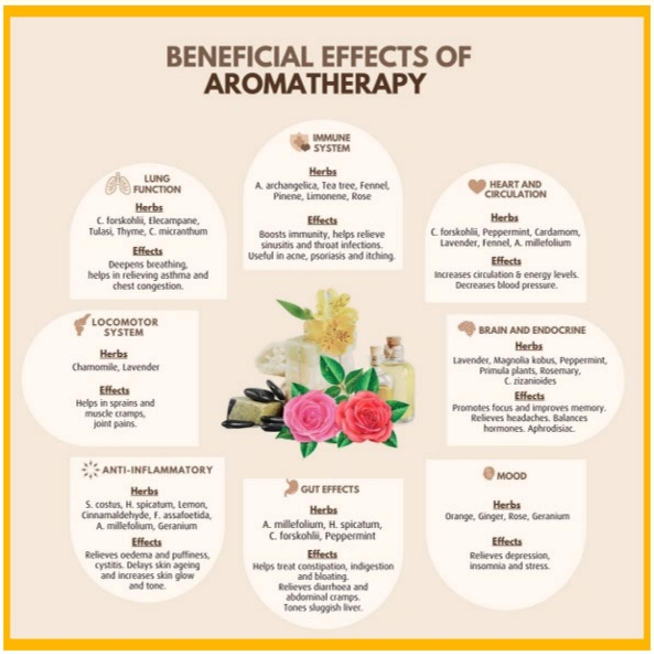

Figure 3: Beneficial effects of likeable aromas on various body systems and functions.

Chandran and Shetty in 2017 investigated the effect of Tulasi arka (distillate) nebulization in patients of Tamaka swasa (COPD) [37]. Distillates are essential oils obtained from the plant parts by the process of heating which causes vaporization, followed by condensation of the vaporized essential oils in a cold chamber. The phytochemical profile of Tulasi (*Ocimum sanctum*) comprises of alkaloids, tannins, glycosides, and saponins. Study results showed that Tulasi arka significantly **improved the vital capacity (VC) of the lungs** by controlling the key symptoms including swasa kashtata, ghurghuraka, kasa, and muhurmuhu swasa.

Cournoyer., *et al*. conducted a meta-analysis in 2022, on the effect of odour stimulations on physical activity. They concluded that certain types of likeable aromas improved some aspects of performance during physical activity, such as cardiac output and precision, by modulating the sensations perceived [38]. These likeable aromas included peppermint, jasmine and lavender. Nagai., *et al*. investigated the effects of inhaling aromas (rose, jasmine and lavender) which were preferred by the participants, on physical exercise in college students [39]. Their results revealed that the inhalation of preferred aromas enhanced physical performance in the college students and athletes, probably by suppression of the muscle sympathetic vasoconstrictor activity, which in turn could reduce overall pain feeling. In regards to sympathetic activity influenced by aromas, essential oils from pepper, estragon, fennel or grapefruit have been found to increase relative sympathetic activity when compared with an odourless solvent (triethyl citrate). On the other hand, essential oils of rose or patchouli decreased relative sympathetic activity by 40% [40].

4. Medicinal effects of essential oils

Most aromatic substances are obtained from plant sources by the process of distillation, which yields the essential oil (EO) in a purified form (see section 3B). EOs are concentrated liquids containing a complex mixtures of various volatile compounds. Specific aromatic compounds obtained by distillation can further be separated by the process of fractionation. The aromatic EOs are often used as fragrances in agarbattis and electric vaporizers, and also in perfumes. Marrelli., *et al*. in 2020 reviewed the effectiveness of essential oils in the treatment of **arthritis** and arthritis-related pain [41]. The reviewers noted that Agarwood EO contains sesquiterpenes and chromones, endowed with several biological properties such as antioxidant, anti-nociceptive, antimicrobial, and antidiabetic. The anti-arthritic potential of Agarwood EO was demonstrated in arthritic rats with significant inhibition in the increase of paw volume by up to 27.88% [42]. EOs of *C. rotondus* and *C. esculenthus* also inhibited paw edema in experimental rats. Essential oil of *Ocimum americanum* contains linalool, 1,8-cineole, camphor, and eugenol, and exhibited antiarthritic potential in zymosan-induced arthritis in mice [43]. Cinnamaldehyde, a key component of essential oils can reduce IL-1β-induced inflammatory cytokine production [44]. Similarly, Eugenol was found to suppress TNF-α, TGF-β, and IFN-γ in arthritic rats [45].

In an interesting study, Meamarbashi in 2014 demonstrated that among healthy male university students, administration of peppermint essential oil resulted in significant improvements in grip strength, jump performance, spirometric parameters, reaction times, and vital signs, including blood pressure, heart rate, and breath rate [46]. These findings suggest that peppermint essential oil could potentially **enhance athletic performance** and respiratory parameters, thereby opening new avenues for sports nutrition and athletic training. Peppermint oil also helps relieve symptoms of **digestive disorders,** coughs, and colds. Aromatic thyme oil is mainly used in the treatment of respiratory disorders. Tea tree oil inhalation exhibited **anti-inflammatory actions** on the immune system in experimented mice [47]. In experimented rats, inhalation of *Ocimum micranthum* EO prevented airway hyper responsiveness caused by antigen challenge, demonstrating its usefulness in respiratory dysfunctions [48]. Aromatherapy patch application aims to treat respiratory infections by continuously releasing volatile components. These adhesive patches incorporate essential oils such as chamomile, wintergreen, peppermint, clove, cinnamon, ginger, lemon, and clary sage, with various biological properties [49].

Olfactory stimulation, by inhalation of essential oils, can affect multiple physiological parameters such as electrodermal activity, blood pressure (BP), pulse rate, muscle tension, and brain activity [50,51]. Hence, EOs from a single plant species can prove beneficial in several disorders. *Coleus forskohlii*, a perennial herb with a pleasing aroma, is effective against various health ailments, including heart conditions, lung diseases, asthma, digestive disorder, liver disorders, skin diseases, muscle spasms, and convulsions [52]. Inhalation of Elecampane EO obtained from its roots, has been found to be associated with improved alertness and brain function, exhibiting therapeutic potential for several psychophysiologic disorders [53]. *S. costus* extracts possess a strong aromatic odour and are highly efficacious in the treatment of kidney, liver, and blood diseases [54]. *C. zizanioides* EO is effective in weight management and skin care [55].

Kumari., *et al*. in 2021 concluded that the essential oils of Hedychium spicatum are rich in alkaloids, protein, carbohydrates, resins, saponins, glycosides, steroids, tannin, flavonoids, phytosterols, and albumin saccharine, contributing to their anti-microbial, immunomodulatory, and hepatoprotective properties [56] Hedychium spicatum has been widely used against asthma, liver-related problems, piles, diarrhoea, constipation, abdominal pain, bronchitis, headache and painful musculo-skeletal conditions. Lunz and Stappen in 2021 reviewed various aromatic root-essential oils and their associated biological activities [57]. Their results confirm the ethnobotanical value of aromatic roots and highlight their potential as important sources of bioactive compounds with a diversity of molecular structure and biological activity. Hudlikar., *et al*. and Sundaram., *et al*. noted that Gluconasturtiin-derived isothiocyanates are aromatic isothiocyanates, possessing **anti-tumour and anti-cancer** activities against lung, breast, colorectal, oral, glioblastoma, prostate, and ovarian cancer [58,59].

5. PHYSIOLOGICAL MECHANISMS OF ACTION (MOA) OF AROMAS

5.1 MOA through modulation of Gaso-transmitters

The term "gasotransmitter" was first coined in 2002 when a team of researchers identified hydrogen sulfide (H_2S) as the third gaseous signalling molecule [60]. Hydrogen sulphide is best known as the "rotten-egg" smelling molecule, and after this discovery, H_2S joined nitric oxide (NO) and carbon monoxide (CO) in the group of small molecules involved in cellular signalling processes. These small, gaseous molecules dictate a wide variety of physiological processes. The gasotransmitters are now known to be activated by several substances, including essential oils. Since several aroma-therapy compounds are obtained from essential oils, it is evident that the aroma-compounds can exert systemic effects through activating gaso transmitters. In other words, one of the mechanisms of action of pleasant smelling oils is through the cellular signalling carried out by gaseous molecules like nitric oxide.

A fine example of this MOA is the physiological action of rose oil in reducing systemic blood pressure. Demirel in 2022 demonstrated through an elegant experiment that rose oil can significantly mediate vasorelaxation in both phenyl-ephrine (PE) and Potassium Chloride (KCl) pre-contracted rat thoracic aortas [61]. The aortas had been previously excised and isolated, and small segments of the aorta were used for the study. The researchers observed that rose oil was able to induce vasodilation in the aortic segments. It was also noted by the researchers that the rose oil-induced vasorelaxant effects were reduced by L-NAME (analogue of arginine, which inhibits NO production) pre-treatment. These results demonstrated that rose oil-induced endothelium-dependent vasodilation is mediated by the NO-cGMP-dependent pathway. In other words, inhalation of rose oils can facilitate in reducing high blood pressure by facilitating the action of NO.

It is well known that the sulphur compounds present in vegetables go through enzymatic or chemical transformations in the human body, forming hydrogen sulphide (H_2S). It is also acknowledged that the consumption of cruciferous vegetables, which contain sulphur compounds, is associated with a reduced risk of breast, lung, colon, bladder, and prostate cancer [62]. The significant antinociceptive properties of the EO of the seed of Ferula asafoetida (EOSF) in mouse models, have been attributed to peripheral anti-inflammatory activity and central opioid pathways [63]. Bagheri., *et al*. in 2020 demonstrated that EOSF is capable of inhibiting the growth of the AGS (adenocarcinoma gastric) cell line [63]. EOSF contains organosulphur compounds, such as Alpha-D-Xylofuranoside, E-1-propenyl sec-butyl disulfide, Z-1-propenyl sec-butyl disulfide, and methyl 2,5-di-Omethyl. Previous studies have shown that organosulfur compounds up-regulate the activity of various metabolizing enzymes, such as glutathione S-transferases, involved in the detoxification of carcinogens, and inhibit the formation of DNA adducts in target tissues [64]. These H_2S forming compounds have exhibited good chemopreventive effects [65].

Essential oils also have the capacity to inhibit nitric oxide production, and because of this property, are able to exert antioxidant, anti-inflammatory, antibacterial and anti-proliferative actions. The following examples show-case the deleterious effects that Nitric oxide (NO) can produce in the body, and how essential oils can inhibit the production of this gaso transmitter. Citrus peel essential oil has been shown to inhibit the NO production induced by LPS (lipo polysaccharide) in RAW264.3 (macrophage cell line) cells by 42.5% [66]. This is the probable mechanism of action of the excellent anti-inflammatory activity of citrus essential oils. Trans-cinnamaldehyde compounds found in the essential oils of the leaves of *Cinnamom osmophloeum* exhibit beneficial effects against bacteria, pathogens, mosquitoes, termites, mites, fungi, and mildew [67,68]. Tung., *et al*. in 2010 demonstrated that the leaf essential oils of cinnamaldehyde suppressed NO synthase in lipopolysaccharide-activated RAW 264.7 macrophages, thereby causing an antiinflammatory effect [69].

Similarly, *Achillea millefolium* (found in the Himalayan region) is effective against inflammatory disorders, hepatobiliary conditions, spasmodic pain, gastrointestinal and cardiovascular diseases, and also respiratory disorders [70]. The extracts of A. millefolium extracts have shown excellent anticancer activity in diverse tumor cell types [71-73]. A. millefolium essential oil can inhibit the inflammatory response of lipopolysaccharides (LPS)-stimulated RAW 264.7 macrophages, by causing reduced superoxide anion and cellular nitric oxide (NO), and decreased glutathione (GSH) and lipid peroxidation [74].

Microglia activation leads to the production of pro-inflammatory compounds such as nitric oxide (NO), reactive oxygen species (ROS), and reactive nitrogen species (RNS). Nitric oxide (NO) is a crucial mediator of neuronal cell death and inflammatory response. When NO reacts with a superoxide anion, it generates peroxynitrous acid and peroxynitrite, which are highly toxic. Due to a strong association of NO with the aetiology of neurodegenerative diseases, inhibiting NO synthesis has been considered a potential therapeutic target for treating these disorders such as Alzheimer's disease and Parkinson's disease. A study conducted by Elmann., *et al*. in 2010 showed that Geranium oil, popularly used in aromatherapy, can inhibit NO production and expression of the proinflammatory enzymes cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in microglial cells [75]. These anti-neuroinflammatory effects suggest the application of Geranium EO in the treatment, amelioration, and prevention of neurodegenerative diseases.

5.2 MOA through Activation of Extra Sensory Olfactory Receptors

Though the sense of smell primarily resides in the nose, the receptors for olfaction are, surprisingly, present in several other non chemosensory organs and tissues of the human body. Aromas can therefore influence the bodily systems and functions in locations remote from the head via these extra-sensory olfactory receptors. Maberg and Hatt discovered in 2018 that when olfactory receptors in the nose are stimulated by specific aromas, similar receptors present at several extra-sensory sites in the body are also stimulated by them, exerting multifarious systemic effects [76]. In the cardio-vascular system, Olfactory Receptors (ORs) have been found to be expressed in the human aorta and coronary arteries. The odorant, Lyral, is able to activate these ORs present in the vessels, evoking an intracellular Calcium influx and the phosphorylation of protein kinase B (AKT), which results in enhanced migration and **angiogenesis** [77]. The latter can have an impact in coronary artery disease. The ORs in the heart have also been found to have chronotropic and ionotropic effects.

Moreover, olfactory receptors have been identified in the skin, where these receptors increase the regeneration of skin cells and help speedy **wound healing** [78]. The smell receptors in the liver, when activated, may even decrease the **spread of cancer** cells [79]. ORs have also been identified in the male gonads, where the testicular ORs participate in **sperm motility** and chemotaxis. Tong., *et al*. showed that human sperms exhibited elevated swim speeds and well-directed movements responding to bourgeonal, a flowery compound which has been found to be the most powerful agonist of OR1D2 [80]. They postulated that cAMP-mediated Ca^{2+} signal may be responsible for this bourgeonal induced cellular response. Spehr., *et al*. 2003, in their path-breaking study on the presence of ORs in human spermatozoa, concluded that hOR17-4 has a significant role in the function of human sperm chemotaxis and may be a critical component of the fertilization process [81].

In muscle tissue, the olfactory receptor sub-type Olfr16 is believed to have an important function in skeletal muscle regeneration and myofiber branching. Decreasing Olfr16 levels through electroporation (application of electric current) of Olfr16 siRNA resulted in aberrant regeneration [82]. Tong., *et al*. demonstrated that α-cedrene **stimulates myogenesis** and prevents *in vitro* atrophy of myotubules induced by free fatty acid. α-cedrene is a natural sesquiterpene component found in cedarwood oils and is used as food additive for flavour enhancement [83]. The beneficial effects of α-cedrene have been shown to be mediated by Olfr16. Further, α-cedrene administration attenuates muscle wasting in high-fat diet (HFD)-fed mice and increases muscle mass in normal chow-fed mice. Recently, Lee., *et al*. demonstrated that in cultured skeletal myotubes, stimulation of Olfr544 by azelaic acid, a C9 dicarboxylic acid naturally occurring in rye, barley, and other grain foods [84], activates mitochondrial biogenesis and autophagy; these effects of azelaic acid are abolished by Olfr544 siRNA transfection. This could not be observed in olfr544−/− mice [85].

In the Cellular Immune System, OR transcripts have been identified in several types of human blood cells, such as erythrocytes, peripheral blood mononuclear cells (PBMCs), natural killer cells, B and T lymphocytes, and neutrophils [86-89]. Further, ORs discovered in human immune cells can affect chemotaxis and activation of key cells like macrophages. Dairy butter contains aroma compounds, that are known ligands for a variety of class I ORs that are expressed in various blood cell types [87]. These aroma compounds bring about chemotactic behaviour in human neutrophils [90]. Scents have also been shown to inhibit chemokine-driven chemotaxis in CD4 T cells, and can regulate macrophage function in murine immune cells [91,92]. The smell receptors in the immune system have also been observed to promote the death of certain types of leukaemia cells [79].

5.3 Actions of Aromas mediated through the Olfactory Tract

Olfactory stimuli, after being received by olfactory neurons, are conveyed to the olfactory tract. The olfactory tract is a conglomerate of structures that connects the olfactory bulb to parts of the cerebral cortex (Figure 4). This results in a direct connection between the sensory input from the olfactory neurons and the olfactory cortex [93]. The olfactory bulb (OB) is an ovoid structure located in the anterior cranial fossa, right above the cribriform plate of the ethmoid bone, and under the frontal lobe of the brain. It receives axons from the olfactory receptor neurons (ORNs) located in the olfactory region of the nasal cavity. These axons pass through the cribriform plate of the ethmoid bone, and converge into the olfactory nerves that project directly to the ipsilateral olfactory bulb.

Thousands of these axons of ORNs synapse with the principal neurons of the OB, called mitral and tufted cells. These synaptic regions are known as glomeruli. The olfactory tract is initially formed by the axons of mitral and tufted cells as they exit the caudal end of the olfactory bulb [94], and run along the olfactory sulcus on the orbital surface of the frontal lobe. These axons forming the olfactory tract then attach to the base of the brain at the anterior perforated substance [93,95]. Here, the olfactory tract divides into the medial and lateral olfactory striae [93,96].

While the multipolar neuronal fibers of the medial stria travel to the septal area, other fibers in the medial stria cross the anterior commissure and excite granule cells in the contralateral olfactory bulb [96]. The lateral olfactory stria is the principal central projection pathway for the olfactory system [95]. It travels along the surface of the temporal lobe in the vicinity of the uncus, and terminates almost entirely in the primary olfactory cortex. A small portion, though, reaches the amygdala [95].

The primary olfactory cortex comprises the piriform lobe of the anterior part of the temporal cortex, an area that includes the cortical part of the amygdala, the uncus, and the anterior end of the parahippocampal gyrus [95,96]. These sites, after receiving the olfactory information, send projections to the hypothalamus, hippocampus, amygdala, and the thalamus [95]. The olfactory cortex also projects to the ventral part of the striatum, including the Nucleus Accumbens and the Olfactory tubercle [97-99]. The striatum is part of the basal ganglia, which form a section of the limbic system [100].

There are several important structures within the limbic system, including the amygdala, hippocampus, thalamus, hypothalamus, basal ganglia, and cingulate gyrus [101]. The Limbic system participates in several different mental and psychological functions, such as emotion, behaviour, motivation, long-term memory, and olfaction [102]. Importantly, the pleasure centre, which is involved in sexual arousal and in the "high" derived from certain recreational drugs, is located in the limbic system. Considering that many of these parts of the limbic system are directly or indirectly supplied by the olfactory impulses, it stands to reason that aromas and odours can directly impact the psychological functions mentioned above. Since a fraction of the projections from the olfactory tract also reach the immediate vicinity of the hypothalamus and the pituitary, these master endocrine organ of the body can also be affected by fragrances.

5.4 Action of aroma compounds through direct entry into brain

Aroma molecules can directly access the brain substance and act by attaching to receptors on neuronal surfaces. The molecules can enter the brain through two routes – via the lymphatics, and along the fibrils of the sensory nerves, primarily the olfactory nerves. These routes are explained below.

ROUTES OF ENTRY OF AROMAS THROUGH THE NOSE INTO THE BRAIN

5.4A. Lymphatic route through the Cribriform plate

The nose is unique in respect to its being the only site where the brain can interact with the outside environment [103]. Nerve fibrils of the Olfactory nerve extend directly from the olfactory bulb in the brain to the olfactory region of the nasal cavity. The nasal cavity is divided anatomically into three regions : vestibule, respiratory and olfactory (Figure 4). The olfactory region is richly supplied by the Olfactory nerve, and is the primary area for perceiving smell. The nerve filaments of the olfactory nerve (axons), numbering in millions, penetrate the mucosal lining of the nasal cavity and are in direct contact with the environment without any relaying sensory receptors. In other words, the olfactory neurons directly act as odour sensors.

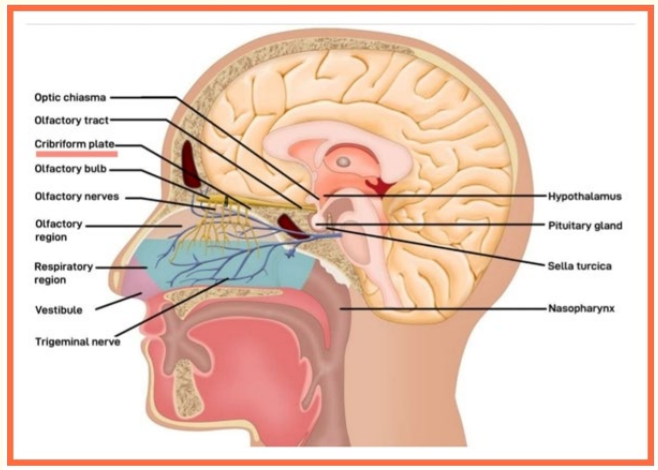

Figure 4: The cribriform plate provides direct access to the brain, since the inhaled fragrance compounds can either travel in the peri-neural space of the nerve fibrils of the Olfactory nerve, as well as be transported through the lymph channels running between the nasal mucosa and the cranial cavity through the cribriform plate.

The nerve fibrils of the olfactory neurons enter the cranial cavity through the perforations in the cribriform plate, which is situated in the roof of the nasal cavity. Alongside these nerve fibrils are present very fine lymphatic vessels, which communicate between the nasal mucosa and the brain lymphatics. This recently discovered lymphatic system of the brain, located in close proximity to the dural venous sinuses, has been found to communicate with the lymphatics of the neck and the nasal mucosa [104]. The communicating lymphatic channels of the neck run alongside the vessels and nerves that enter and exit the cranial cavity. This is also the case with the lymphatics that travel along the olfactory nerve fibres, and this latter lymphatic route is now being extensively researched to utilize the nasal route for drug delivery. The valve-free nature of lymphatic channels, coupled with capillary action, allow the lymph in the nasal mucosa to enter the cranial cavity and reach the brain tissues with ease. Several studies have established that by utilizing the olfactory/nasal lymphatic route, intranasally administered lipophilic drugs can be delivered expeditiously to the

CSF and can then disperse to brain tissue through the dynamics (including CSF-ISF exchange) of central nervous system fluids [105]. The brain being mainly a lipoidic organ (composed of around 80% lipid), the brain cells can then avidly take up any oily or aromatic molecules which have reached the brain through the nasal lymphatics. These fragrant and incense molecules can then exert their actions smoothly and efficiently.

5.4B. Nerve and epithelial route through the cribriform plate

The cribriform plate is a part of the ethmoid bone and lies between the Olfactory region of the nasal cavity and the brain. The olfactory bulbs and olfactory tracts are located in the vicinity of the cribriform plate [106]. The epithelium of the Olfactory region of the nasal cavity is unique, since it is a specialized neuro-epithelium, and contains three types of cells, including the olfactory neural cells. These neuronal cells originate in the olfactory bulb and terminate at the apical surface of the olfactory neuroepithelium. Odour molecules, especially lipophilic (hydrophobic) compounds, can be taken up by these neuroepithelial cells, either by passive diffusion, or by endocytosis. On the other hand, hydrophilic molecules can be taken up by the paracellular route, through the inter-cellular junctions. While the absorbed lipophilic aroma molecules can travel along the axons to the olfactory bulb, the hydrophilic compounds can proceed to the brain within the perineural space present along the olfactory nerve fibrils. This peri-neural space is lined by plain epithelial cells [107].

Since the axons of the olfactory neurons run uninterruptedly from the olfactory region of the nasal cavity to the brain (Figure 4), this trans-cellular route is now being extensively explored as an intra-neuronal pathway to deliver drugs directly to the brain. The average diameter of olfactory axons in humans is about 0.1–0.7 μm, hence molecules or nanoparticles having diameters within this range can be readily delivered through this pathway to the olfactory bulb, and thence into the olfactory cortex. From the olfactory cortex, the aroma compounds can travel to the caudal pole of the cerebral hemisphere and into the cerebrum and the cerebellum. Over the last decade, more than a hundred animal studies have been conducted that testify to the fact that low molecular weight compounds as also larger peptides can directly be transported from the nose to the brain tissue [103]. The time taken for this transport has also been quantified. Agrawal., *et al*. 2018, and Gänger and Schindowski., 2018 have reported that drug delivery through the olfactory nerve took around 1.5–6 h, while delivery through olfactory epithelial cells was achieved within a few minutes [108,109].

The fifth cranial nerve, called the Trigeminal nerve, is divided into three branches and each branch connects to the brain stem and olfactory bulb [109,110]. The respiratory region of the nasal cavity is supplied by the trigeminal nerve which is mainly sensory, and conveys pain and temperature sensation from the face, nasal cavity and oral region to the brain. The nasal epithelium is richly invested with peptidergic nociceptors, which respond to numerous odorants as well as irritants. These peptidergic trigeminal sensory fibers also enter the glomerular layer of the olfactory bulb [111]. Therefore, drug and aroma delivery to the epithelium supplied by the trigeminal nerve can also be a direct route of drug delivery from the nasal cavity to the brain (Figure 4). Although most of the trigeminal nerve enervates the respiratory region of the nasal cavity, some trigeminal nerve fibres are also present in the olfactory region [109]. Thus, drugs reaching the trigeminal nerve fibres in both the respiratory and olfactory regions can directly reach the brain.

Taking together all the above studies, it can be surmised that the nasal route is a quick and effective route for aroma compounds to access the brain. Though the fragrance molecules are transported mainly through the axons of the olfactory nerve fibrils supplying the olfactory region of the nasal cavity, some amount of transport can also be carried out through the nerve fibres of the Trigeminal nerve supplying the respiratory region.

6. Benefits of practicing *Pranayama* in a Fragrant Environment

Pranayama is an ancient Yogic practice consisting of breathing exercises. These breathing techniques range from very simple ones, such as Anulom Vilom (alternate nostril breathing) to very complicated ones. But even the simplest ones like Anulom-Vilom, performed for 5-10 minutes a day, yield remarkable results, by affecting the autonomic nervous system [112]. Practising these breathing exercises in a fragrant ambience, using specific aromatic oils and distillates, can further enhance the beneficial effects of the pranayama. In fact, the synergistic effects of pranayama and aromatherapy can plausibly multiply the health gains accruing from these modalities. The fragrant environment can be easily

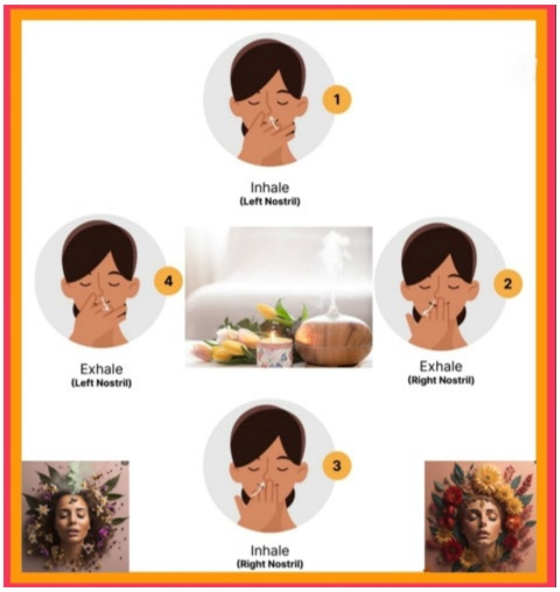

Figure 5: Yogic breathing exercises, such as Anulom-Vilom shown here, can yield even better results if practiced in a fragrant environment.

created by burning incense sticks or by using electrically operated aroma dispensers (Figure 5).

7. Effect of Aromas on Neurogenesis

Neurogenesis (NG) in adult mammals is prominently observed in two specific brain regions: the subventricular zone (SVZ) and the subgranular zone (SGZ) of the hippocampal dentate gyrus. Neurons born in the SVZ migrate through the rostral migratory stream (RMS) to the olfactory bulb (OB), where they differentiate into interneurons (Figure 6). This migration is important for the sustenance and functional adaptation of the olfactory system, which is unique by virtue of its constant turnover of sensory receptor cells, which are in fact neurons (see section 5.4B). The olfactory system, by its very design, maintains a direct link with the areas of the brain responsible for identifying odours, controlling behaviour, and modulating emotional responses, making it a key component in the sensory-behavioural paradigm influencing adult neurogenesis. This is credible since odours can influence the migration of neuronal stem cells to the olfactory bulb (OB) and, consequently, affect neurogenesis.

Odours, once detected by the olfactory epithelium, initiate a complex series of neuronal activations, leading to the migration of neural progenitors from the SVZ to the OB [113]. This migration is influenced by the olfactory environment, since enriched olfactory environments have been shown to enhance neurogenesis in the OB by promoting the survival of newly born neurons [114,115]. Conversely, olfactory deprivation can lead to a decrease in the survival rates of these neurons during critical developmental windows [116]. Moreover, the role of odours extends beyond the physical migration and integration of neurons; it also includes functional aspects such as learning and odour discrimination. Studies have shown that olfactory learning tasks can modulate the survival rate of newly born neurons in the OB, indicating a selective process that might be based on the function or engagement of these neurons in odour-related tasks [117,118].

The continuous influx of new neurons into the OB is essential not just for replacing older neurons but also for optimizing olfactory discrimination. The ongoing neurogenesis ensures the OB's adaptability to new odours or complex olfactory environments, thereby maintaining the efficiency and precision of the olfactory system [117,119,120]. The selective survival and integration of these neurons are likely influenced by their exposure to specific odours, indicating a feedback loop where olfactory experiences regulate the neurogenic process. These key findings highlight the significance of sensory experiences in shaping the brain's structure and function, including neurogenesis. It shows an interesting aspect of neuroplasticity, where environmental stimuli directly influence the regeneration and integration of neurons in brain areas.

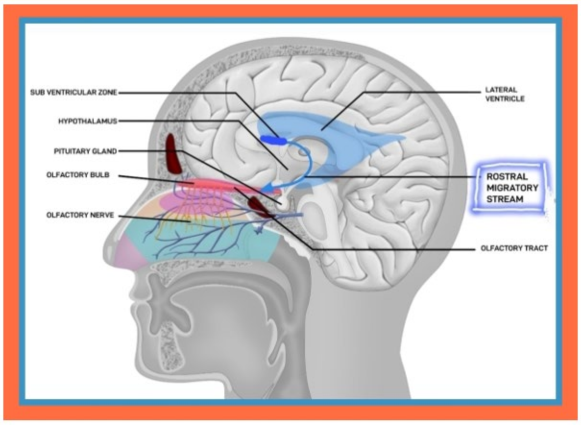

Figure 6: The most important region of the brain for neurogenesis, is the sub-ventricular zone. From here, the newly created neurons migrate along the Rostral Migratory Stream, to the olfactory bulb, replenishing the worn-out and dead neurons in the bulb.

Discussion

Fragrance compound producing plants are a valuable natural resource with an impact on both physical and mental health via the effects on olfaction [121]. Fragrances can be enjoyed using a number of delivery modalities, such as incense sticks, perfume sprays, vaporizers, and scented bath salts. Along with the numerous researchers mentioned in preceding sections, Ali., *et al*. in 2015 explored the therapeutic role of aromatherapy in the treatment of many diseases [122]. They found that inhaling rosemary and other floral essential oils was associated with improved locomotor activity in mice [123]. Aromatherapy also has a calming effect on the mind and body by promoting the release of serotonin and endorphins [124]. Plants that are commonly used in aromatherapy include jasmine, neroli, rose, bergamot, lime, sweet orange, lemon, tangerine, mandarin, cinnamon, lemongrass, patchouli, petitgrain, palmarosa, rosemary, geranium, lavender. The rejuvenating, spiritual, and physiological effects of aromatherapy can be effectively applied in the treatment of central nervous system disorders, during both acute and chronic stages. Furthermore, it is now recognized that Parkinson's disease (PD) is associated with either complete loss or a diminished sense of smell; hence, it appears conceivable that decreased neurogenesis, resulting in an inability to replace the senile olfactory neurons, is one important aspect of the aetiology of PD. Improving or stimulating neurogenesis may thus prove to be an important modality to stave off PD, and maybe even reduce the symptoms.

The Mahamrityunjaya Mantra alludes to pleasant smells (sugandh) as health enhancers. This is clearly expressed in the second line of the mantra, which states : Sugandhim pushti vardhanam. The meaning of the three words separately is : Sugandhim = aroma, perfume ; Pushti = health, well-being; Vardhanam = enhance, increase. Read together, the three words mean "Aroma enhances well-being". It may be relevant to recount here the advice given by the Vedic-era Rishi Vashisht to the boy Markanda, who was destined to die at the very young age of 16 years [125]. In his desperation to evade death, Markanda had asked the learned Guru Vashisht for advise. The Guru instructed the lad to undertake penance under a Bhadra-vat (Banyan tree) located on the banks of the Bhadra river, using perfumed flowers as offerings to the Lord. The boy did as instructed, and was able to vanquish death itself. This episode highlights the great importance of fragrant compounds and aromas on health and longevity.

In the ancient Ayurvedic text Ashtanga Samgraha, it has been explained that Nasa (nostril) is the door way to Shira (head), and the drug administered through nostrils reaches Shringataka by Nasasrota and spreads in the Murdha (Brain)) taking the route of Netra (eye), Shrotra (ear), Kantha (throat) and Siramukhas (opening of the vessels) [126]. Nasa being the Sanskrit word for nostrils, and srota being source, Nasasrota may be interpreted as " the source of entry " of drugs into the brain. Figures 1 and 3 show how the olfactory pathway is intimately associated with some of the areas of the brain responsible for transmission of visual information (optic chiasma). Acharya Sushruta, in his treatise Sushrut Samhita, has clarified Shringataka Marma as a Sira Marma formed by the union of Siras (blood vessels) supplying the nose, ear, eye and tongue. According to the commentator Indu, the exact Sthana of the Shringataka marma is "Shiraso Antarmadhya Murdha" which can correspond to the middle cranial fossa. On the basis of above information, the meaning of the verse "Nasa hi Shirsodwaram" becomes abundantly clear, signifying that the nostrils are the portals of entry into the brain, as regards medicinal compounds administered via the nose [126]. The elaborate discussion in section 5.4 explicitly analyses and validates this postulate of Acharya Sushruta.

Apart from the common means of delivering aroma compounds enumerated in the beginning of this section, another manner of administering medicinal compounds nasally, is through the performance of havans. Havan is a sacred ritual wherein oblations are proffered to the fire-god. In this practice, various pulverized substances like Guggul (*Commiphora wightii*) and Giloye (*Tinospora cordifolia*), Chandan (*Santanum album*), Kapoor (*Cinnamomum camphora*), are tossed into the fire which is ignited in a receptacle (fire pit) using diced wooden pieces, and kept burning by use of ghee (clarified butter). Since ghee is being used along with the herbal mixture, some of the phytochemicals in the herbs which have volatilized due to the heat, get hitched onto the ghee molecules in the smoke. On inhaling the smoke, these phyto-compounds, carried by lipid ghee particles, can get adherent to the nasal epithelium, since the cell membrane of the epithelial cells is almost entirely composed of lipids. After adsorption by the nasal neuro-epithelial cells, the phytochemical molecules may be carried along the nerve axons, or get transported directly through the cribriform plate to the brain, as explained in section 5.4. These bioactive compounds can then reach the hypothalamic- pituitary axis, thus exerting actions on the master endocrine glands of the body, which in turn affect almost all body systems, by activating other "stimulating" hormones.

Conclusion

Aromatherapy has been in use worldwide for a long time, to provide relief from mental and physical ailments. The Indian scriptures go a step further, and regard the proper use of fragrances as being reinvigorating, and capable of successfully resuscitating even a critically ill patient. This is explicit from the verse of the Maha Mrityunjaya Mantra (the mantra which can avert death), which clearly states, "Fragrance promotes health". Since the cribriform plate provides a route for direct access to the brain, essential oils and perfumed compounds can easily reach the brain when administered intra-nasally. Further, the close proximity of vital brain centres, such as the hypothalamus, pituitary and basal ganglia, to the olfactory tract, allows the olfactory signals and inhaled aromatic molecules, to significantly influence the functions of these brain regions. Used appropriately, aromas can boost the health status, improve cognition and memory, balance the mood and promote longevity.

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