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Review Article

Aromatherapy in Early-Stage Cancers

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Abstract

The therapeutic use of essential oils to treat illness and promote physical, emotional, and spiritual well-being is known as aromatherapy. Odor stimulation in a closed system with a low concentration of α-pinene, a bicyclic monoterpene in the essential oils of pine trees, induces a significant increase in parasympathetic nervous activity, thereby causing physiological relaxation in young adult females. Long-term exposure to similar conditions suppresses melanoma growth in mice. When the diluent is triethyl citrate (TEC; mw:276), which is used as a solvent and fixative in fragrances, long-term exposure to low levels of odorants, such as α-pinene, alcohols, phenols, ketones, and their derivatives, in an open system may activate glomeruli clustered in the lateral domain of the rat dorsal olfactory bulb (alcohol/phenol-responsive domain) and could increase hypothalamic β-endorphin levels and inhibit certain types of cancers. Meanwhile, μ-opioid receptors in cancer are involved in regulating the malignant transformation of tumors and participating in proliferation, invasion, metastasis, and angiogenesis. Notably, μ-opioid receptor expression in transgenic mice with breast cancer was observed on larger growing tumors but not on the very small, early tumors. The regulation of stress levels through the modulation of β-endorphin via aromatherapy could not only improve disease progression and promote a sense of well-being in patients, but also provide alternative pharmacological treatment for very small, early tumors.

Keywords: Aromatherapy; Odor; Early-Stage Cancers; β-Endorphin; μ-Opioid Receptor

Introduction

A seven-fold increase in the μ-opioid receptor in cell lines of human lung cancer has been observed [1]. When samples from patients with metastatic lung cancer were separated from a cohort of all lung cancer patients, μ-opioid receptor expression increased approximately two-fold [1]. Tumors expressing high levels of μ-opioid receptors are associated with higher rates of perineural invasion and worse cancer outcomes [2]. μ-Opioid receptors are involved in regulating the malignant transformation of tumors and participating in proliferation, invasion, metastasis, and angiogenesis [3,4]. On the other hand, the early detection of cancer or precancerous lesions and medical intervention hold great promise for improving patient survival rates [5]. In particular, predicting the tissue of origin of early-stage cancers using a serum miRNA profile could improve patient prognosis [6]. Notably, μ-opioid receptor expression in transgenic mice with breast cancer was observed on larger growing tumors but not on very small, early tumors, suggesting that the tumor microenvironment, also known as the tu-

mor immune microenvironment, contributes to μ-opioid receptor expression [7,8]. β-Endorphin is an endogenous opioid peptide that acts as an agonist for opioid receptors with a high affinity for the μ-opioid receptor [9-11]. β-Endorphin is involved in potent analgesic effects, reward-centric behaviors, and homeostasis-restoring behaviors [12]. There are two functionally distinct systems for the release of β-endorphin: one for peripheral effects via systemic circulation, and one directed to the central nervous system using synaptic communication and additional volume transport mechanisms provided by the flowing cerebrospinal fluid [12,13]. In the former system, the β-endorphin is called plasma, peripheral, or circulating β-endorphin, while in the latter system, the β-endorphin is called hypothalamic or cerebrospinal fluid β-endorphin. Although there is evidence that peptides such as β-endorphin can penetrate the blood–brain barrier to a degree, peripheral and central cerebro-spinal fluid levels of β-endorphin are not necessarily related [12]. When the hypothalamus releases corticotroponin-releasing hormone in response to physiologic stressors, the anterior pituitary gland receives the signal to synthesize and store β-endorphin [14]. Plasma β-endorphin is most likely to be excreted in response to postoperative pain [14,15]. Meanwhile, in the central nervous system, β-endorphin binds to μ-opioid receptors, inhibiting the release of the inhibitory neurotransmitter, GABA, and causing excess production of dopamine [14]. The essential oils used in aromatherapy suppress cancer-associated pain, strengthen the immune system, and produce anti-stress effects [16]. Odor stimulation with a low concentration of α-pinene in a closed system has been shown to activate the parasympathetic nervous system in young adult females and induce physiological relaxation [17]. In general, long-term exposure to a low concentration of odorants, such as alcohols, phenols, ketones, and their derivatives, may increase rat hypothalamic β-endorphin levels relative to those in control [18,19]. This review describes the increase in rat hypothalamic β-endorphin levels due to the long-term exposure to a low level of odorants in an open system, parasympathetic nerve-mediated cancer suppression, and the anti-cancer effects of β-endorphin.

Long-term exposure to odorants that activate glomeruli clustered in the lateral domain of the rat dorsal olfactory bulb may increase hypothalamic β-endorphin levels

Under long-term exposure to odor stimulation with a low concentration of α-pinene in a closed system, the melanoma tumor volume of mice was about 40% smaller than that in control mice [20,21]. α-Pinene very strongly activated glomeruli clustered in the lateral domain of the rat dorsal olfactory bulb (alcohol/phenol-responsive domain) [22], which may reflect parasympathetic nerve activity [17], likely increasing hypothalamic β-endorphin levels [18,19]. Because α-pinene is highly volatile, these experiments were conducted in a closed system in which air containing a low concentration of α-pinene was flowed at a constant rate [17,20,21]. Open-system experiments using these odorants have also been conducted to provide odor stimuli more easily [18,19]. Figure 1 shows odorants (1-14) that significantly increased rat hypothalamic β-endorphin levels (ng/mg protein) after long-term exposure (10 h/day, 7 days) in an open system compared with a control group [18,19].

Figure 2 shows the relationship between the percentage increase (%) in rat hypothalamic β-endorphin levels due to long-term exposure to odorants compared with a control group in an open system and the odorant molecular weight (mw).

Long-term exposure to a low concentration of geranyl linalool (1, mw:290), a straight-chain diterpene alcohol with a very weak green floral aroma, in an open system increased rat hypothalamic β-endorphin levels by approximately two-fold compared with a control group (see Figure 2) [19]. When the diluent was ethyl alcohol in an open system, guaiacol (13, mw:124) and cis-3-hexenol (14, mw:100), which are highly volatile odorants with molecular weights of less than 150, rapidly evaporated into the atmosphere; therefore, rat hypothalamic β-endorphin levels did not increase compared with the control group [19]. On the other hand, when the diluent was TEC in an open system, long-term exposure to low

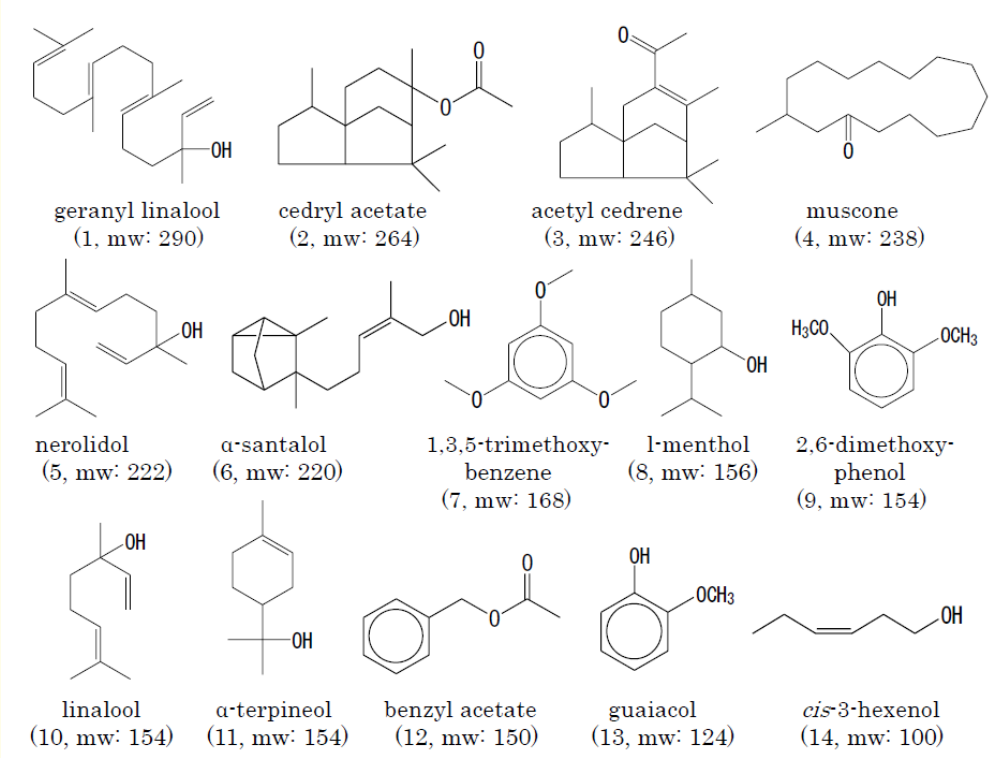

Figure 1: Odorants (1-14) that increase rat hypothalamic β-endorphin levels with long-term exposure in an open system [18,19].

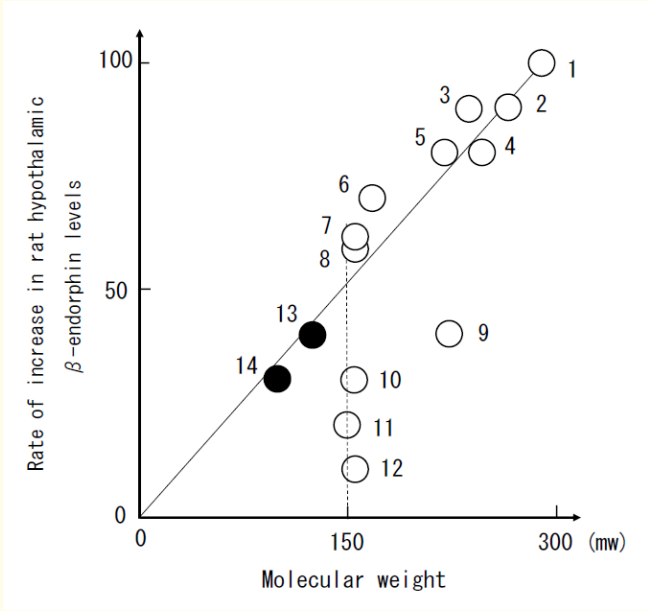

Figure 2: The relationship between the percentage increase (%) in rat hypothalamic β-endorphin levels due to long-term exposure (10 h/day, 7 days) to odorants in an open system compared with a control group and the odorant molecular weight (mw). Diluent: ethyl alcohol (○); TEC (●). See Figure 1 for odorant number.

concentrations of guaiacol (13, mw:124; ●) and cis-3-hexenol (14, mw:100; ●), which have lower molecular weights than α-pinene (mw:136), significantly increased rat hypothalamic β-endorphin levels compared with the control group (see Figure 2) [19]. Galangal, patchouli, sandalwood, spikenard, and borneol oils showed significant sedative effects on mice, and this effect was stronger for a mixture of the five oils than for any of the single oils [23]. This suggests that the odorant mixture might have a synergistic effect on increasing rat hypothalamus β-endorphin levels. In aromatherapy for suppressing certain types of early-stage cancers, it should also be considered that many odorant receptors are expressed in tumor cells and may be associated with cancer progression [24,25].

Parasympathetic nerve activities decrease tumor growth and metastasis in certain experimental models

Adrenergic signals consistently exert protumorigenic effects, whereas acetylcholine is a neurotransmitter in parasympathetic neurons, and cholinergic signaling plays different roles in cancer progression depending on the tumor type [26,27]. While the parasympathetic/vagal nerves have cancer-promoting effects on prostate, gastric, and colon cancer and small cell lung carcinoma, they have cancer-suppressing effects on pancreatic and breast cancers [28]. Vagus nerve stimulation evokes widespread systemic and neural epigenetic effects through DNA methylation and histone modification on a number of pathways involved in stress response signaling, inflammatory cascades, and other homeostatic/endocrine pathways [29]. Action potentials originating in the parasympathetic nerve regulate T cells, which in turn produce the neurotransmitter required to control innate immune responses (acetylcholine) [30,31]. The vagus nerve can significantly and rapidly inhibit the release of macrophage tumor necrosis factor, thereby attenuating the systemic inflammatory response [32,33]. The vagus nerve is the only pathway that transmits parasympathetic signals between the brain and thoracoabdominal organs, thereby exerting an anti-inflammatory function via the cholinergic anti-inflammatory pathway [34]. It appears that vagus nerve signaling regulates the immune response dynamics against disseminated tumor cells within milky spots and inhibits the development of peritoneal metastases [34].

Anti-cancer effects of β-endorphin

β-Endorphin blocked the expansion of human ovarian keloid fibroblast cancer cells in vitro; this effect was counteracted with naloxone, which is an opioid antagonist [35,36]. β-Endorphin can enhance some immune reactions, such as the lymphocyte proliferative response to mitogens both in vivo and in vitro, or the cytotoxic activity of NK cells [37]. Hypothalamic β-endorphin neurons suppressed preneoplastic lesion development in a 1,2-dimethylhydrazine-induced rat colon cancer model [38]. 1,2-Dimethylhydrazine induced tumors in the colons of control rats at 100% incidence but failed to induce colonic tumors in 70% of animals with β-endorphin neuronal transplants [38]. Early postoperative syndrome in cancer patients is characterized by a marked increase in plasma β-endorphin levels regardless of the type of surgery [39]. On the other hand, chronic pain syndrome in incurable patients is accompanied by decreased plasma and cerebrospinal fluid β-endorphin levels [39]. β-Endorphin, primarily through its interaction with μ-opioid receptors, attenuates stress responses and reduces pro-inflammatory cytokine levels while simultaneously increasing anti-inflammatory cytokine levels [12]. The regulation of stress levels through the modulation of β-endorphin could not only improve disease progression and promote a sense of well-being in patients, but also provide an alternative pharmacological treatment for tumor growth and development [40]. Plasma β-endorphin levels in patients with ovarian cancer [41] or breast cancer [40] have been shown to be significantly lower compared with a control group. Statistically significantly positive correlations were reported between survival time/disease-free time and plasma β-endorphin levels in patients with ovarian cancer [36,41]. Higher plasma β-endorphin levels were observed in patients with ovarian cancer without recurrence of the neoplastic process than those with recurrence [41]. In patients with squamous carcinoma of the head and neck, β-endorphin regulated the immune system and increased the production of the leukocyte migration inhibitory factor, reaching almost normal levels [36]. Immune cells containing β-endorphin migrate to inflamed tissue in a site-directed manner [42]. β-Endorphin is released in inflammatory environments and is rapidly biotransformed to generate various pharmacologically active fragments [42].

Comparison of the effects of β-endorphin (an endogenous opioid) and morphine (an exogenous opioid) on immune responses

Low doses or the short-term use of opioids can have a positive effect on the immune system [37,43,44], whereas long-term use or high doses of opioids may induce the opposite effect [7]. The administration of a small dose of morphine (0.5 mg/kg) enhanced NK cell cytotoxicity in pigs four-fold compared with saline [37]. In a rat model of bone cancer pain, recombinant rat β-endorphin (50 μg/kg) and plant source morphine (10 mg/kg) were administered intraperitoneally every other day for 15 days to evaluate the differences in analgesic effects and cellular immune functions [45]. Treatments with β-endorphin and morphine had good analgesic effects on bone cancer pain, while the analgesia provided by morphine was stronger than that of β-endorphin [45]. Morphine treatment reduced the spleen T cell growth rate and the content of T cell subtypes (CD3+, CD4+, and CD8+ cells), whereas β-endorphin administration increased T cell proliferation, NK cell cytotoxicity, and the relative quantities of T cell subtypes [45].

Analgesic effects of β-endorphin for nociceptive cancer pain

Pain is an early symptom of cancer and often leads to a cancer diagnosis, but it can also be a significant source of distress for patients as the disease progresses [46]. β-Endorphinergic neurons in the hypothalamic arcuate nucleus synthesize β-endorphin to alleviate nociceptive behaviors [47]. β-Endorphin that is released by T cells under inflammatory conditions activates opioid receptors on nerve endings, thereby inhibiting the release of substance P and pain reception via sensory neurons [11]. Conversely, pain relief itself is speculated to regulate plasma β-endorphin levels, serving as an objective measure of cancer pain severity and corroborating patient reports of pain relief [48]. The lower the pain in primary liver cancer patients, the higher the plasma β-endorphin level [49]. Plasma β-endorphin levels increased with improvement in pain in patients with upper abdominal gastrointestinal malignancies [48]. The use of peripherally acting opioids for the prolonged treatment of inflammatory pain associated with cancer is not necessarily accompanied by opioid tolerance [50]. The continuous presence of endogenous opioids might preserve μ-opioid receptor signaling and thereby counteract the development of tolerance [47,50]. Therefore, the direct promotion of endogenous β-endorphin synthesis may provide an avenue for the development of analgesia without tolerance [47].

Conclusion

Aromatherapy may be a complementary therapy for early-stage cancer patients. These findings suggest that aromatherapy could also be used by cancer patients who have undergone treatments such as chemotherapy, radiation therapy, surgery, and immunotherapy to reduce the risk of recurrence and support recovery and well-being. Developing products such as cosmetics, masks, and bedding containing odor molecules that increase hypothalamic β-endorphin levels could provide an avenue for the development of analgesia without tolerance and also lead to new therapeutic approaches for certain types of early-stage cancers.

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Informed Consent Statement

The author read and approved the final manuscript.

Data Availability Statement

Not applicable.

Conflicts of Interest

The author declares that they have no conflicts of interest.

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