

# Essential Oils and Terpenes

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Essential oils have been used in multiple ways, i.e., inhaling, topically applying on the skin, and drinking. Thus, there are three major routes of intake or application involved: the olfactory system, the skin, and the gastro-intestinal system. Understanding these routes is important for clarifying the mechanisms of action of essential oils. Here we summarize the three systems involved, and the effects of essential oils and their constituents at the cellular and systems level. Many factors affect the rate of uptake of each chemical constituent included in essential oils. It is important to determine how much of each constituent is included in an essential oil and to use single chemical compounds to precisely test their effects. Studies have shown synergistic influences of the constituents, which affect the mechanisms of action of the essential oil constituents. For the skin and digestive system, the chemical components of essential oils can directly activate gamma aminobutyric acid (GABA) receptors and transient receptor potential channels (TRP) channels, whereas in the olfactory system, chemical components activate olfactory receptors. Here, GABA receptors and TRP channels could play a role, mostly when the signals are transferred to the olfactory bulb and the brain.

Keywords: essential oils ; routes ; olfactory system ; skin ; gut-intestine

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## 1. Introduction

The history of using essential oils as the medical treatments or as the supplements to medical treatments goes far back to the ancient time in Egypt, which is even several thousand years ago. Depending on the countries and the cultures, essential oils have also been used in the religious ceremonies and for the relaxation for similarly long time period. This long history of using essential oils in the cultural events and the relaxation has most likely affected the images of essential oils in many people even still nowadays in a way that they are 'mysterious' or 'just for the relaxation', which presumably had disturbing influences to consider them as the subjects of scientific endeavor.

The beginning of 20<sup>th</sup> century has become one of the turning points in the history of using essential oils. René-Maurice Gattefossé, a French chemist who worked at his family-owned perfume company, and not a clinician of holistic, alternative medicine, accidentally burnt his hand because of an explosion in the laboratory. He found that an essential oil of lavender suppressed the pain and the scar formation, which triggered him to start his researches on the essential oils from a chemist's viewpoint and also led him to coin the word 'aromatherapy' <sup>[1]</sup>. The importance of his life-long studies on the essential oils is that he found the roles of terpenes in the effects of essential oils: "Essential oils contain constituents which possess almost the full range of chemical functions. The simplest are hydrocarbons, constituting the terpene family, of the type *p*-cymene, C<sub>10</sub>H<sub>14</sub>, which is similar to pinene, a constituent of oil of turpentine. The other constituents can almost all be classified as various stages in terpene development" <sup>[1]</sup>. This can be called the starting point of the scientific studies on the effects of essential oils.

It has been already one century since then. There are increasing number of scientific studies on the effects of essential oils especially during the last few decades. Studies have found that essential oils have the effects on brain functions such as improving/decreasing cognitive function, depending on the types of essential oils <sup>[2][3]</sup>, and some studies have found their effects on suppressing anxiety <sup>[4]</sup>. There are also studies showing their anti-nociceptive, anti-inflammatory, anti-convulsant, anti-oxidant, and anti-bacterial effects <sup>[5][6][7][8][9][10][11][12][13][14]</sup>. Studies using the chemical constituents included in essential oils have shown that there are chemical compounds that have anti-cancer, anti-bacterial, anti-viral, anti-inflammatory, anti-oxidant influences, and also these that enhance wound healing by improving cell proliferation and cell migration <sup>[15][16]</sup>. These studies indicate that essential oils can affect the central nervous system and also the peripheral system at cell levels. Such diversity in the influences suggests that essential oils may activate separate routes: these related to the signaling pathways related to the brain functions and these related to the signaling pathways related to the cell proliferation and cell migration, and apoptosis, and thus longevity of cells, in the peripheral systems.

The diversity in these effects makes us also consider whether the multiple types of methods in using essential oils have some roles. Essential oils are used 1) by inhaling, which will use mostly the olfactory system and to some extent the skin as the chemical compounds will reach the skin. 2) By topically applying essential oil on the skin, in which the major route will be through the skin and to a lesser extent through the olfactory system as the aroma will reach the olfactory system. 3) By drinking, in which the major route will be through the digestive system and, secondarily, because of the retro-nasal location of the nose, through the olfactory sensory system, as the aroma will reach the nose from the mouth and stomach. It is possible that, depending on the way of using essential oils, they activate different routes and, depending on the routes activated, they produce different effects. It is necessary to take into consideration how the essential oils were applied when the effects of essential oils were studied.

## **2. Through the olfactory system**

Studies of essential oils using the method of inhalation are testing the influences through the olfactory system in main. Considering that the olfactory system has routes directly to the brain, this could be the pathway that affects brain functions.

Studies so far using essential oils have shown that there are differences in the impacts depending on the types of essential oils. For example, when human subjects were exposed to the aroma of lavender (*Lavandula angustifolia*) or ylang-ylang (*Cananga odorata*) through a diffuser, their working memory decreased and the reaction time was slower in the tasks that required memory and attention, whereas the aroma of rosemary (*Rosmarinus officinalis*), peppermint (*Mentha piperita*), common sage (*Salvia officinalis*), and Spanish sage (*Salvia lavandulifolia*) enhanced their performances <sup>[21][31][17][18]</sup>. The mood of the subjects were also more alert and more active and 'fresher' when they were exposed to the aroma of rosemary (*Rosmarinus officinalis*) than the lavender (*Lavandula angustifolia*) <sup>[21][31][17]</sup>. These results suggest that it would be better to use lavender (*Lavandula angustifolia*) and ylang-ylang (*Cananga odorata*) for relaxation, and peppermint and rosemary in enhancing alertness and memory function.

Where are the aromas of the essential oils detected in the nasal cavity? Studies on the olfactory system of mice have found that there are multiple regions in the nasal cavity, which are involved in the olfactory sense: the main olfactory epithelium, the vomeronasal organ, the septal organ of Masera, and the Grüneberg ganglion <sup>[19][20]</sup>. In addition, there are separate sensory receptors expressed in other sensory neurons that reside in the main olfactory epithelium or the vomeronasal organ but carry different receptor types. These are the receptor guanylyl cyclase (GC-D) <sup>[21]</sup> and trace amine-associated receptors (TAAR) <sup>[22][23]</sup> in the main olfactory epithelium and formyl peptide receptors in the vomeronasal organ. In case of humans, most likely, the main olfactory epithelium is the single functional olfactory system. The main olfactory epithelium is located at the upmost region in the nasal cavity. It is the area, which is closest to the brain, where the olfactory epithelium spreads on the nasal turbulence. In case of mice, there are about 1000 different types of olfactory receptors <sup>[24][25]</sup>, whereas in case of humans, there are less than 400 <sup>[25][26][27][28]</sup>. Each olfactory neurons carry a single type of olfactory receptor, which enables the olfactory system to distinguish odors. The olfactory receptors are not homogeneously distributed in the olfactory epithelium, but instead, they are split in the areas constructing 4 zones' structure <sup>[29][30]</sup>. In addition, a new neural cell adhesion molecule, known as the olfactory cell adhesion molecule (OCAM), was found and the expression of OCAM showed zone differences, i.e., negative in Zone 1 but positive in Zones 2 to 4 in the main olfactory epithelium and in the main olfactory bulb (MOB), and positive in the apical region of the vomeronasal organ and the rostral region of the accessory olfactory bulb (AOB) but negative in the basal region of the vomeronasal organ and caudal AOB <sup>[30]</sup>. Based on these findings, the names of Zone 1 to 4 of the olfactory epithelium are often called the Dorsal domain (Zone 1; OCAM negative) and the Ventral domain (Zones 2 to 4; OCAM positive). The axons from the olfactory neurons, which carry the same olfactory receptors, assemble at the MOB and generate a glomerulus. Recent studies have determined the types of odors and the locations of the glomeruli related to these odors in the olfactory bulb <sup>[31]</sup>. The glomeruli related to terpenes were found to be located in the ventral domain of the olfactory bulbs <sup>[31]</sup>. This area is where the axons from the lateral/ventral areas reach, and this suggests that the area where terpenes in essential oils are sensed in the olfactory epithelium could be the lateral/ventral areas which project their axons from sensory neurons to the ventral domain of the MOB. This hypothesis is partially supported using three types of terpene compounds, cavone, 1,8-cineole, and limonene. 1,8-Cineole and limonene generated responses in the lateral/ventral part of the olfactory epithelium whereas the responses to cavone included the dorsal region and the lateral/ventral region <sup>[32]</sup>.

### 3. Through the skin

There are multiple types of receptors present in skin that can be involved in the pathways activated by the chemical constituents included in the essential oils: the olfactory receptors expressed in skin, the cannabinoid receptors (CB receptors), and the transient receptor potential channels (TRP channels).

The olfactory receptors expressed in the non-olfactory system including skin are not involved in the olfactory sense. There are some differences in their functions depending on the locations they are found, but so far they are found to be involved in the chemical reactions like chemotaxis [33], adjusting blood pressure [34], and stimulating secretion of enzymes [34]. The tissues/organs or cells that these olfactory receptors in non-olfactory system were found are sperm cells [33][35][36], testes [36][37], heart [38], kidney [39], skin [40] and gut/intestine [34][41][42][43].

Recent studies have found that human olfactory receptor OR2AT4 is expressed in the epidermis of the skin, with the strongest expression in the basal layer, stratum basale, and that OR2AT4 becomes activated by sandalore, a synthetic sandalwood (*Santalum*) odorant [40]. Activation of OR2AT4 stimulated cell proliferation and migration, activation of cAMP-dependent pathways, and phosphorylation of extracellular signal-regulated kinases (Erk1/2) and p38 mitogen-activated protein kinases (p38 MAPK). OR2AT4 was later found to be expressed in the outer root sheath of hair follicles. Stimulation of OR2AT4 by sandalore suppressed apoptosis and extended hair growth and longevity [41][44], which suggests another possible use of OR2AT4, i.e., in avoiding thinning of hair.

Another human olfactory receptor, OR51E2, was found in human epidermal melanocytes [45]. The ligand of OR51E2 was  $\beta$ -ionone, which is an aroma/odorant included in, for example, rose (*Rosa*) essential oils. Activation of OR51E2 by  $\beta$ -ionone stimulated melanin synthesis, suggesting the possibility of utilizing it in the “treatment of pigmentation disorders and proliferative pigment cell disorders such as melanoma” [46].

Human olfactory receptors OR2A4/7 and OR51B5 are also expressed in human skin and they are activated by the odorants cyclohexyl salicylate and isononyl alcohol, respectively [47]. Cyclohexyl salicylate has a rather strong flowery fragrance and is used in, for example, shampoos, shower gels, and soaps. Locations of expression of OR2A4/7 and OR51B5 were slightly different, although both were expressed in the epidermis: OR2A4/7 was expressed in keratinocytes in the supra-basal epidermis (stratum spinosum) and in the melanocytes in the basal layer (stratum basale), whereas OR51B5 was found expressed only in the keratinocytes of the supra-basal layer but not in the basal layer of the epidermis. Their impacts were also different. OR2A4/7 stimulated cytokinesis, cell migration, regeneration of keratinocytes, phosphorylation of AKT and Chk-2, and secretion of IL-1, whereas OR51B5 stimulated cell migration, phosphorylation of Hsp27, AMPK1, and p38MAPK, and secretion of IL-6.

These studies have shown that, although there are some differences in the locations of expression and functions of these olfactory receptors, all of them similarly stimulate cell proliferation and cell migration when they become activated by their ligand aroma-odorants. In the morphology of skin, there are two areas, the basal epidermis and the upper bulge of hair follicles, where stem cells are produced to maintain skin homeostasis and hair regrowth, respectively. The results suggest the possibility that essential oils with the ligands for these olfactory receptors may become new clinical agents to enhance skin homeostasis and hair regrowth.

$\beta$ -caryophyllene is a sesquiterpene included in various spice and herbs. For example, essential oils of oleoresin (*Copaifera paupera*) and lavender (*Lavandula angustifolia*) are well known to have beta-caryophyllene in them. It has a smell, thus activates olfactory receptors, and recently it was found to be a ligand of cannabinoid receptor 2 (CB2) [48]. Recent studies have shown that topical application of  $\beta$ -caryophyllene improves re-epithelialization in the cutaneous wounds [49]. Essential oils of oleoresin (*Copaifera paupera*) which contains  $\beta$ -caryophyllene have shown the same effect [50]. RNA sequencing and pathway analyses of skin exposed to  $\beta$ -caryophyllene showed that the pathways related to cell proliferation and cell migration were significantly activated (the sonic hedgehog pathway, the planar cell polarity signaling pathway, the fibroblast growth factor signaling pathway, and the Wnt  $\beta$ -catenin signaling pathway) [49]. Studies have found that hedgehog signaling is involved in epidermal homeostasis [51] and that sonic hedgehog secreted from sensory neurons surrounding the hair follicle bulge stimulates Gli1+ (a hair follicle bulge marker) cells in the upper hair follicle bulge to convert to multipotent stem cells which will migrate to the epidermis and contribute to re-epithelialization [52]. These studies suggest that  $\beta$ -caryophyllene application improves re-epithelialization through enhancing the conversion of hair follicle bulge stem cells into multipotent stem cells and stimulating their migration towards the basal epidermis, and, from there, towards the wound bed. This is the first study showing the effects of a chemical constituent of essential oils at the level of gene expressions and molecular analyses.

## 4. The gut and intestine

Much less have been studied focusing on the influences of essential oils through the gut and intestine. There are some recent studies, which have found that the chemical compounds in orange essential oils, *i.e.*, limonene, linalool, and citral, enhance the microbiota, especially *Lactobacillus*, in the gut of mice, and limonene had the strongest impact <sup>[53]</sup>. The olfactory receptor for limonene, Olfr56 (human homolog, OR2V1) <sup>[54][55][56][57]</sup>, is expressed in both the large intestine as well as in the small intestine in mice. Olfactory receptor Olfr78 (human homolog, OR51E2) was also found expressed in some, but not all, of the enteroendocrine cells in the colon of mice, and propionate was found as their ligand <sup>[42]</sup>. In a separate study, Olfr78 responded to acetate and propionate <sup>[34]</sup>. Propionate is an important nutrient generated by bacteria, which stimulates secretion of satiety-inducing hormones that can adjust energy homeostasis <sup>[57]</sup>. These studies suggest that essential oils may be involved in regulating energy homeostasis by enhancing the microbiota, which will stimulate the secretion of propionate, which is the ligand of olfactory receptors. We still need more studies in detail to determine the influences of chemical constituents included in essential oils.

## 5. Factors that affect the effects of essential oils and terpenes

Despite the long history of using essential oils, there have been rather few scientific studies on them. Needless to say, there have been few studies taking consideration on the routes (olfactory, skin, gut-intestine), receptors, gene expressions, and signaling pathways that they generate the effects. What is important in the studies on odorous chemicals is the specific cautions required in handling them so that the conditions are precisely controlled. Odorous chemical compounds have certain volatility, and, depending on their volatility, the concentration can easily change quickly in the samples used for tests. Depending on the type of material used in preparing/diluting the samples, the chemical compounds can also attach to the surface of the container easily, which will make the concentration decreased in the samples to be tested. It is also necessary to know the purity of the samples and what else are included, if the purity is less than 99.9%, because the small portion of the other chemical compounds may affect the results.

When the whole essential oil, and not the single chemical compound, is used in the studies, the possibilities of differences in the combination of chemical compounds included and the differences in their percentages can be much larger than using single chemical compound. Although there are some essential oils with rather small numbers of chemical compound constituents (for example, about 25 in the case of guaicawood (*Bulnesia sarmienti*) oil), most essential oils have 100 to 250 different chemical compound constituents, and some contain 300 to 400 <sup>[58]</sup>. In the very popular lavender (*Lavandula angustifolia*) and rosemary (*Rosmarinus officinalis*) oils, studies have identified 505 and 450 chemical compounds, respectively. Comparison of the major constituents of the same essential oil in several studies shows that the chemical compounds listed as major constituents vary. The amount of these major constituents varies depending on the part of the plant used, *e.g.*, old leaves versus young leaves, different seasons, geographical locations, and even the weather depending on the year. This makes it critical to measure the constituents of the essential oils used in experiments, to control the exposure methods (inhalation vs. capsule digestion vs. topical application) as well as to state the environmental conditions which can affect the exposure (temperature, humidity, air flow). The data also indicate the importance of testing the effects of pure single chemical compounds contained in essential oils. This will make experiments comparable and help to determine the influences of each chemical compound and the concentration dependency of its effect.

These factors are what we need to take into consideration when we work with essential oils and terpenes. Studying the effects of essential oils and terpenes will require interdisciplinary approaches because of the multiple methods of their use: diffusers, which will use the olfactory system primarily; drinking, which will use primarily the digestive system; and topical application, which will enter primarily through the skin. Experimental techniques in olfactory neuroscience, skin biology, and small intestine physiology will allow testing the effects of the essential oil constituents, which are likely to be different depending on the application routes. The vast number and types of herbal plants necessitates interaction with plant biologists. Handling the constituents of essential oils requires knowledge and techniques in analytical chemistry.

Now have more scientific evidence on, *e.g.*, the anti-inflammatory, analgesic, and anti-microbial effects at the chemical compound level compared to the effects of complete essential oils. Understanding the effects of each constituent and combinations of constituents in *in vivo* and *in vitro* studies may lead to the development of new medical agents for wound healing, bacterial infection, and healing of other diseases, including cancer. It is time to thoroughly test and determine the large potential of terpenes in essential oils in order to improve health conditions because of their impacts on the olfactory system, the skin, and the gastro-intestinal system.

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