Biological Effects of Fragrances and Essential Oils

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Fragrance compounds and essential oils have been known since ancient times for their healing properties. Nearly all cultures had the knowledge of fumigating sick persons. Aromatic plants were used for their pleasant or invigorating odors to freshen sick rooms. And we are very familiar with the word perfume which is derived from the Latin per fumum.[1-4] The historical uses of fragrances in medicine have been reviewed by the author recently,[1] therefore a repetition here is not necessary.

Nevertheless it is worth noting that essential oils are very heterogeneous mixtures of single substances—presently we have identified more than 3,000 compounds.[4] Hence one has to be aware that biological actions are primarily due to these single substances in a very complicated concert of synergistic or antagonistic activities. Essential oils are not "the soul of the plant," as someone has called this group of phytochemicals romantically, but totally unscientifically.[5,6] These are chemicals created by nature with all the benefits and disadvantages that a chemical substance possesses. Mixtures of such chemicals therefore show a broad spectrum of biological effects.

This article will deal mainly with the mode of action of essential oils and fragrances. It is also necessary to express an opinion on the dispute over whether the observed effects are generated only by a pleasant feeling that is via a reflectorial way, or by a direct molecular interaction of the fragrance molecule with a receptor.

But again it should be stressed that essential oils are mixtures of many single substances. These compounds seem to possess:

- a distinct molecular formula,
- a certain molecular weight (roughly between 100 and 300 amu and therefore are rather small molecules), and
- certain physicochemical properties like polarity, electron density, optical activity, etc.

This means that the biological activity of fragrance molecules can be compared with the activity of drugs, and therefore their pharmacological aspects should be investigated. It is unscientific to act any other way!

It is an interesting fact that in spite of the broad applicability of essential oils, especially in phytotherapy, very little is known about the mode of action. Some scientists[7] think of an unspecific action principle (because of glaring similarities between the lipophilic, water insoluble and very volatile essential oils with inhalation narcotics) which more or less acts upon the peripheral nervous system and relaxes the smooth muscles. Experiments proving a correlation between decreasing water solubility and the increasing efficacy of some constituents of essential oils seem to be in accordance with this theory.

Today the excellent skin permeability of essential oils by means of their high lipophilicity is a proven fact. A good to excellent resorption takes place not only through mucosas of mouth, nose,[8] pharynx and the gastrointestines, but also through intact skin.[9,10] For instance, α-pinene could be detected in the exhalation air within 20 min after resorption. Many other terpenic compounds were exhaled shortly after this time. Experiments performed at the Munich Institute of Balneology and Climatology proved that terpenes had a 100-fold better skin permeability than water.[11] There exists a sort of steady state, because the terpenes get resorbed and eliminated continuously into and out of the blood vessels.[12]

The findings recently published by Buchbauer and his group are in agreement with these results.[13] After a massage with 1 g of 2% solution of the essential oil of lavender in peanut oil, the volunteer's blood was taken and the concentration of the main constituents, namely linalool and linalyl acetate, was determined in the plasma. Within a few minutes after finishing the massage, the first nanograms of these compounds were detected, with a maximum concentration detected at about 20 min. Within 90 min most of the lavender oil was eliminated. These findings show clearly not only the lipophilic nature of the fragrance compound itself, but also the acceleration of the dermal penetration by the massage with a fatty oil.

Considering the above mentioned effects one easily discerns that the lipophilic character of fragrance compounds is mainly responsible for the broad spectrum of biological activities. Their easy passage through the blood-brain barrier is also due to their lipophilic nature. Their affinity towards lipid-rich tissues like those of the central nervous system (CNS) facilitates an exchange of fragrance molecules from blood into such lipid tissues.

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Recently, a detailed study on the mode of action of essential oils has been published.[14] The influence of apolar synthetic compounds on the generation of a spontaneous potential and on the conductivity of nervous cells is well documented. Such compounds get better integrated into membrane systems of the cells when their lipophilicity is higher. This integration leads to an increase in the membrane volume because of an interruption of the interaction of the membrane lipids with one another. As a result it brings about an electrical stabilization of the membrane. This leads to an inhibition of the inflow of calcium ions. It also leads to the suppression of the increase of permeability for sodium ions, which is necessary for a release of the action potential. By this cascade of reactions, a narcosis or a local anesthesia is induced, depending on the type of the compound and the manner of its application. Higher concentrations decrease the conductivity of potassium ions. At the highest concentrations cell damage and lysis could be observed.[15] Finally it should be remembered that some authors also discuss an interaction of such membrane-active compounds with protein kinase C, which is an enzyme and should have an influence on the spontaneous rhythm of cardiac and nerve cells.[16]

Thus a lot of biological effects of essential oils and fragrance compounds can be explained. The constituents of the essential oils, the aroma chemicals, accumulate in the nerve cell membrane, thus causing a sterical blocking of embedded function proteins, which are the ion channels. This blocking causes a change in the physical properties of the membrane, especially a modification of its ion permeability. An inhibition of the inflow of calcium ions leads to a spasmolysis. Suppressing the generation of an action potential causes a local anesthesia. And the suppression of the irritability of mast cells, which are responsible for inflammation, brings about an anti-inflammatory effect.

In this context it is important to note the concentration of the fragrance compounds, their application method, rate and degree of resorption, distribution in the body, and their bio-transformation. According to the above mentioned detailed study,[14] it is generally supposed that essential oils reaching cells in high concentrations evoke unspecific effects, in particular irritation by destruction of cell membranes. On the other hand, fragrance compounds reaching cells in very low concentrations, according to their physicochemical properties and their molecular shapes, get integrated in special areas of cell membranes and evoke specific effects by influencing the enzymes, carriers, ion channels and receptor proteins, which are localized in these areas.

Bringing these cognitions into focus, it is nonsense to apply aromatherapy by massage. Massage application of aromatherapy is wrong mainly because of the high concentration in which the fragrant molecules reach the cells and evoke unspecific effects. On the other hand, aromatherapy applied in the correct way by inhalation only (where the resultant plasma concentrations of the aroma compounds are 100- to 10,000-fold smaller) leads to the desired specific effect.

Finally, another point should be mentioned. Essential oils are very complex mixtures of various aroma chemicals. Each constituent contributes to the biological effect of the mixture. Synergistic as well as antagonistic actions are observed. A good example for such an antagonism seems to be the essential oil of rosemary which has, as main constituents, the bicyclic ether 1,8-cineole and the monoterpene α-pinene.[7] 1,8-Cineole, also known as eucalyptol, exerts a spasmolytic effect on an isolated guinea pig ileum, on which contractions had been induced by acetyl choline. On the other hand, the hydrocarbon α-pinene induces a distinct spasmogenic effect. Therefore, depending on the content of eucalyptol in rosemary oil, varying extents of spasmolysis can be observed. The content of this ether depends on the origin of the plant and on its harvesting time. And this is true for all main bioactive constituents of all essential oils.

Such a spasmolytic effect is observed on the smooth musculature which covers the walls of cavity organs such as the stomach, the bronchia, and the intestines, and which is mainly responsible for the maintenance of a continuous potential. Contractions of the smooth musculature can be evoked either by neurotropic or by musculotropic mechanisms. Even if a neurotropic influence of fragrance compounds on the excitation transmittance by neurotransmitters is possible, some monoterpene derivatives, such as fenchone or carvacrol, inhibit enzymes like the acetylcholinesterase which inactivate the spasmogenic acetylcholine. However, more findings argue in favor of a musculotropic inhibition mechanism.

A necessary precondition for contraction of a smooth muscle seems to be an increase of the calcium ions in cell concentration. Therefore, an inflow of these ions from extracellular compartments enormously favors the contractibility and hence the disposition towards spasms. On the other hand, an inhibition of this inflow of calcium ions from the extracellular compartment into the smooth muscle cell protects it from contractions. Some essential oils (like peppermint oil) and their constituents (like menthol, for instance) act in this sense as modulators of the calcium-ion-channel-functions and therefore cause a distinct spasmolysis.[17]

Some therapeutic applications of essential oils and fragrances should be mentioned here also. In an excellent paper Schilcher presented a detailed list of biological effects of essential oils.[18] Essential oils and fragrance compounds should be applied because of their expectorating, appetizing, choleretic, cholekinetic and carminative, spasmolytic, antiphlogistic, antiseptic and disinfectant, diuretic, sedating and stimulating (heart, circulation) properties. Schilcher also mentioned some other effects of essential oils which suit this type of internal application, and furthermore suggested six external uses.[18] Among these properties, the last two are especially in the domain of real aromatherapy, the incorporation or uptake of fragrance compounds only by inhalation.[1-3]

Concerning the mode of action of such fragrance compounds, there are two opposing views. The followers of the reflectorial effect theory believe that fragrance compounds bring the desired effect by creating a sensation of a pleasant feeling and by stimulating the olfactoric nerves which end in the right brain hemisphere, where they connect to the limbic system. The limbic system is responsible for all our emotions and sensations like anxiety, fear, feeling of wellness, harmony and sexual desires. The supporters of the systemic effect theory, on the other hand, believe that the fragrance compounds work by direct molecular interactions with corresponding receptors in the CNS.

Surely a certain part of our psychosomatic disorders and sick feelings is curable by a psychic influence, a psychological treatment and by means of fragrances. Such an aromatherapeutic or osmotherapeutic treatment no doubt has its benefits.[1,2,19-21] The stimulation of medullary centers by fragrance compounds acts also by reflective influence via the *nervus olfactorius*.[4] It is common practice to revive a fainted person by this method.

On the other hand several studies proved the existence of a systemic mode of action. For instance, Ammon answered the question concerning the stimulating effect of rosemary oil.[22] His findings are in favor of a direct interaction of some constituents of this oil with the CNS and dispute the assumption of merely a stimulation of the limbic system via the olfactoric nerves. Also, the fact that odors exert CNS effects outside awareness is a strong argument in favor of the systemic way. A significant alteration of human brain activity has been observed in the EEG dissociated from the perception of detectable odors. Like anosmic persons, the volunteers in this study were not aware that they had inhaled a fragrance, and therefore the changes in the EEG curves (especially β- and θ-waves[24]) cannot be explained by a reflective influence, based only on a pleasant feeling. The absence of any change in motor times across tests and sessions in a series of computer-based reaction-time tests which were performed while inhaling the essential oil of lavender is an additional argument in favor of a direct influence of the fragrance compounds on the cells in the cortex, where such a difference in the decision time could be observed quite well.[3]

Finally, two other pieces of evidence for a direct interaction have been furnished by Buchbauer and his coworkers.[25,26] According to the aforementioned lipophilicity, in a series of inhalation experiments with mice, it could be shown that the greater the lipophilic character of a fragrance compound, the better the sedation of test animals. This is especially surprising considering the difference of activity of alcohols and their more lipophilic esters. For instance β-phenylethyl alcohol showed neither an activating nor a sedating influence on the mice, whereas its ester, β-phenylethyl acetate, proved to be one of the most effective sedatives among the fragrance compounds tested.[26]

And how would one explain the variety of effects created by steric differences, if not by a molecular-receptor interaction of the fragrance compounds? Both the borneol and isoborneol are such an example. Both exhibit more or less similar camphoraceous odor and both show a more or less similar volatility, but the steric orientation of the functional (osmophoric) group, the hydroxyl group, is different and therefore the biological effect is also different. Borneol did not exhibit any noteworthy influence on the motor behavior of the test animals, whereas isoborneol seemed to be one of the most potent activators among the tested fragrance compounds.[26] Can such a difference in activity be explained merely by a pleasant feeling and thus by a reflectorial effect?

In conclusion, at present it seems to be established knowledge that fragrance compounds do possess a distinct pharmacological efficacy besides their good odor, which is mainly due to their lipophilic nature. As far as we know they interact with certain membrane lipids, thus causing among other effects, an alteration of the calcium-ion-channel-function. Besides this direct molecular method of action, the limbic system is also addressed to a certain extent. It is like the double efficacy of taste. If one eats a piece of sugar, one not only senses a sweet and pleasant feeling (which is valid especially for babies) but the ingested sugar molecules induce the whole cascade of insulin reactions also. And why should fragrance molecules not act similarly via a molecular interaction as well as by producing a pleasant feeling?

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