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## Abstract

The positive impact of essential oils and compounds has been known for a long time. Essential oils are multicomponent mixtures and obtained by steam distillation of leaves or flowers or simply by pressing orange peels for example.

Due to the broad-spectrum activity, essential oils can be used for a variety of disorders like sleeping problems, colds or gastrointestinal complaints. The focus of this paper is the use of essential oils in palliative care, hospices and against pain. Essential oils are usually absorbed orally, transdermally or inhalatively.

In palliative care and hospices massages with aroma oils are very helpful to enhance people's sense of well-being. By the gentle touch of a massage or the pleasant scents – body and soul are benefiting. Essential oils may also be used in oral care, for example to treat Candida infections, xerostomia or mouth malodour. Furthermore, they can be used to control nausea or vomiting in cancer patients caused by chemotherapy. The broad use of analgesics like NSAIDs against headaches or menstrual cramps for example, is often associated with unpleasant side effects. Essential oils may help to reduce the analgesic doses.

## Zusammenfassung

Die positive Wirkung von ätherischen Ölen und den in ihnen enthaltenen Komponenten ist schon lange bekannt. Ätherische Öle sind Vielkomponentengemische, die durch Wasserdampfdestillation von z. B. Blättern oder Blüten oder durch Auspressen von beispielsweise Orangenschalen gewonnen werden. Durch das vielseitige Wirkspektrum können sie bei den verschiedensten Indikationen, wie z. B. Schlafstörungen, Erkältungskrankheiten oder Magen-Darm-Beschwerden erfolgreich eingesetzt werden. In dieser Diplomarbeit wird auf die Anwendung von ätherischen Ölen in der Palliativmedizin und Hospiz sowie gegen Schmerzen näher eingegangen. Die Aufnahme von ätherischen Ölen kann oral, inhalativ aber auch transdermal erfolgen. In der Palliativmedizin und Hospiz ist die Massage mit aromatischen Ölen eine gute Möglichkeit, um das Wohlbefinden der Patienten zu steigern. Zum einen durch die angenehmen Düfte und deren Wirkung auf den Körper aber auch durch die Berührungen der Massage selbst. Ätherische Öle können auch in der Mundpflege, z.B. bei Infektionen mit *Candida albicans*, Mundtrockenheit oder Mundgeruch verwendet werden. Bei Krebspatienten können sie Übelkeit und Erbrechen vermindern. Der breite Einsatz von Schmerzmitteln, wie beispielsweise NSAIDs, sei es bei Menstruationsbeschwerden oder bei Kopfschmerzen, ist oft mit einer Vielzahl an Nebenwirkungen verbunden. Durch die Verwendung von ätherischen Ölen könnte die Einnahme von Schmerzmitteln reduziert werden.

# List of abbreviations

| | |
|---|---|
| 5HT | 5-Hydroxytryptamine |
| $A_1$ / $A_{2A}$ receptor | Adenosine receptor |
| ADP / ATP | Adenosine di(tri)phosphate |
| AMPA | α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid |
| APGAR | Appearance, Pulse, Grimace, Activity and Respiration |
| ASA | American Society of Anesthesiologists |
| CB | Cannabinoid |
| cGMP | Cyclic guanosine monophosphate |
| COX | Cyclooxygenase |
| D1/D2 receptor | Dopamine receptor |
| FDA | Food and Drug Administration |
| GRAS | Generally Recognized as Safe |
| HADS | Hospital Anxiety and Depression Scales |
| HIV | Human immunodeficiency virus |
| IASP | International Association for the Study of Pain |
| IL | Interleukin |
| iNOS | Nitric oxide synthase |
| ISPA | International Federation of Professional Aromatherapists |
| LD50 | Lethal Dose, 50 % |
| L-NAME | L-Nitro arginine methyl ester |
| LPS | Lipopolysaccharide |
| M1 receptor | Muscarinic acetylcholine *receptor* |
| MAS | Motion Analysis System |
| NMDA | N-Methyl-D-aspartic acid or N-Methyl-D-aspartate |
| NO | Nitric oxide |
| NSAID | Nonsteroidal antiinflammatory drug |
| PBQ | Phenylbenzoquinone |
| PG | Prostaglandin |
| PIFIR | Pain-induced functional impairment model in the rat |
| POMS | Profile of Mood State |

| | |
|---|---|
| PPT | Pressure Pain Treshold |
| RSCL | Rotterdam Symptom Checklist |
| STAI | State Anxiety Inventory |
| tACPD | Trans-1,3-dicarboxylic acid |
| ToT | Touch or Talk |
| TPPPS | Toddler-Preschooler Postoperative Pain Scale |
| TRP(V) | Transient receptor potential channel (vanilloid) |
| VAS | Visual Analogue Scale |
| WHO | World Health Organisation |

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# *1 Application / Introduction*

There are different forms of application for essential oils. Topically applied the oils are mostly used diluted in carrier oils, like jojoba liquid wax or almond oil for example, which ensure good product distribution on skin and make the massage itself more comfortable. The volatile oils applied to the skin via massage are not only absorbed through the skin but also absorbed via the respiratory tract. Using evaporators or adding a few drops of oil to steaming water can be used for inhalation. Furthermore, a few drops of essential oil can be added on pillows or to bathing water, or mixed in creams or ointments. [1]

**Transdermal absorption**

Human skin is composed of three primary layers, the epidermis, dermis and subcutis. The outermost layer of the epidermis which is called stratum corneum represents a very important barrier and is partly hydrophilic and partly lipophilic. Due to the small molecular weight of essential oils' molecules of below 300 g/mole and their fat-solubility, they diffuse through the skin. Hair follicles, sweat ducts and sebaceous glands also represent entry barriers. Depending on the proportion of volatile molecules (top notes) to larger molecules (base notes) the essential oil is retained in the upper skin layer like in a reservoir. The higher the proportion of volatile molecules the more evaporates into the air. [2]

To increase the absorption, the essential oil is mixed with vegetable oil and applied to a large skin area. Good results can be attained if the skin is fully covered afterwards. Warmth, massage, and hydration of the skin also influences absorption. [3]

**Inhalation**

As essential oils are composed of volatile components, they can enter the body via inhalation either through nose or mouth. From the respiratory tract ending at alveoli the components are absorbed into the bloodstream. The nasal mucosa is very thin and well supplied with blood. Due to proximity to brain, the molecules are able to access the central nervous system, as well as the arterial circulation. The effect on human mood could be explained by the limbic system, which represents the emotional centre of the brain, and the central nervous system. [2]

Inhalation of essential oils stimulates olfactory receptor cells and the impulses are forwarded to the limbic system. The stimulation of this system is determined by the different properties of the various oils and the fragrance. [4]

**Oral intake**

Due to the small molecular weight and the lipophilic properties of essential oils, the components pass through the membranes relatively early in the small intestine when administered orally.

The absorption rate depends on the filling and type of chymus in stomach and intestine. The enriched blood from the intestine gets to the liver via the portal vein and the mesenteric veins. There they are transformed into water-soluble compounds which are then excreted by the kidneys. Depending on the structure of the molecules, the concentration at the site of action varies. [5]

# 2 Palliative medicine and hospices

The WHO (World Health Organisation) uses the following definition:

*"Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." [6]*

This is intended for patients suffering from cancer, HIV, degenerative nervous diseases, cystic fibrosis, muscular dystrophy or other incurable illnesses. A broad multidisciplinary approach that also includes patient's families is necessary to provide effective palliative care.

"Hospice" is defined as a *„care designed to give supportive care to people in the final phase of a terminal illness and focus on comfort and quality of life, rather than cure. The goal is to enable patients to be comfortable and free of pain, so that they live each day as fully as possible". [7]*

For patients and their families, the near proximity of death is difficult to cope with. Many patients live locked in a world of their own and often do not want to talk to others about their feelings, even though communication is important. Aromatherapy and touch may help to cross overcome these barriers. [8]
Gray published that massage is useful for terminally ill patients because the therapeutic touch reaches the patients on both emotional and spiritual level as well as on physical level. [9]

**Mouth Care**

Rohr et al. confirmed that oral discomfort in palliative care patients exerts an influence on the social, physical and psychological well-being. Xerostomia was perceived as a particularly unpleasant symptom. [10]

In fact, a dry or painful mouth, ulcers, cracked lips, and swallowing problems are common symptoms of seriously ill patients. Also fungal infections or mucositis may occur frequently. Dry mouth can have many causes such as increased mouth breathing, the use of drugs such as opioids, sedatives or tricyclic antidepressants, oxygen therapy, chemotherapy, and dehydration. [11]

Kang et al. examined whether essential oils have a positive effect on oral health status in hospice patients suffering from cancer in terminal stage. The experimental group received an essential oil mixture of geranium, lavender, tea-tree and peppermint oil twice a day for one week. Results showed an increase in oral comfort as well as an improvement in objective oral state compared to placebo. Furthermore, the number of colonizing *Candida albicans* decreased. [12]

Especially cancer patients often suffer from oral fungal infections with yeasts, predominantly caused by *C. albicans*. The prevalence of other non-*albicans* yeasts like *C. glabrata, C. tropicalis or C. dubliniensis* is growing. They often show resistance or reduced susceptibility to fluconazole and itraconazol. Cross resistances with the new triazole agent voriconazole were also reported. An effective therapy of these opportunistic infections is an important element of palliative care. Tea tree oil (TTO), which is obtained by distillation of *Melaleuca alternifolia* (Myrtaceae) leaves, has a wide spectrum of antimicrobial activity against *Staphylococcus aureus*, oral bacteria, many fungi and viruses including *Herpes simplex*. In a large-scale study performed by Bagg et al., 301 yeast strains were isolated from the mouths of 199 advanced cancer patients. Fungi and their susceptibility to TTO were analysed by using an *in vitro* agar dilution assay. TTO showed good results, since 41 conazole resistant yeasts were susceptible. Further investigations to assess the antifungal activity of water-based TTO mouthwash *in vivo* are necessary to obtain significant results. [13]

In 2009 Maddocks-Jennings et al. released a randomised and placebo controlled study about the impact of mouthwash with essential oil of *Leptospermum scoparium* (manuka) and *Kunzea ericoides* (kanuka), both Myrtaceae, on mucositis induced by radiotherapy. 19 patients suffering from head or neck cancer were divided into two groups. One group used mouth rinse

containing two drops of a 1:1 mixture of the essential oils in water. The other group gargled with water only. Mucositis symptoms appeared later at the essential oil group and they felt less pain and oral symptoms compared to placebo. [14]

Hur et al. dealt with the effects of TTO, peppermint oil (*Mentha piperita* (Lamiaceae)) and lemon oil (*Citrus limon* (Rutaceae)) on mouth malodour and the production of sulphur compounds. Thirty two intensive care patients received oral cleaning for three minutes using a 2:1:2 mixture of these essential oils on the first day. On the second day benzydamine hydrochloride was used. Malodour was measured by VAS (visual analogue scale) and the production of volatile sulphur compounds was determined using a Halimeter before, five minutes and 60 minutes following treatment. Both parameters were significantly lower when using the essential oil blend. The positive effect of the essential oils on the mouth malodour remained for one hour. [15]

**Wound management**

In 2005 Mercier and Knevitt reported that TTO ameliorated the odour of fungating wounds of cancer patients. This essential oil was diffused during dressing changes or put on the outside of the clothes. If that was not sufficient TTO and an additional essential oil, which was chosen by the patients themselves, were directly applied on the wound using creams at 2.5 to 5 % dilution. [16]

One year later Warnke et al. performed a case series with 30 patients suffering from inoperable squamous cell carcinomas in head and neck. A blend of the essential oils of tea tree, eucalyptus, lemongrass, lemon and clove leaf in a 40 % ethanol base was used to rinse the ulcers twice a day. All participants noticed a removal of the malodour. Several patients experienced either wound healing or even a complete reepithelialisation. [17]

**Cancer**

Cancer is mainly a physical disease but the impact upon patient's life and that of their families should not be underestimated. The diagnosis of cancer mostly triggers strong emotions. [18] Fallowfield suggested that *"both the psychological and the physical consequences of the disease impose a severe threat to the*

*patient's sense of wellbeing and quality of life*". [19] Therefore, effective communication and psychosocial support of professionals with skills in cancer rehabilitation are necessary. Also an essential component of best practice in cancer care are complementary methods such as aromatherapy and massage. Safety of the therapy methods is a very important aspect for cancer patients. The used methods must not harm patient's physical, psychological or emotional feelings. [18]

According to the ISPA Cancer Guidelines for aromatherapists [20] there are several points which should be kept in mind when performing aromatherapy in cancer patients:

- Patients who are undergoing observations or receive therapy for early cancer stages should be treated more carefully regarding the used oil blends. 1 % dilution of essential oil is recommended for topical application.
- In cancer patients undergoing chemotherapy, oils with strong odour as well as the repeated use of the same oils for nausea should be avoided. The risk of an association of nausea with the specific aroma in the future exists.
- In patients receiving radiotherapy, the affected areas should be avoided two weeks before, during, and for six weeks after treatment to ensure healing of the skin and the underlying tissues. Nasal sticks, hand or foot massage could be used instead to reduce anxiety levels.
- Prior surgery a topical application of essential oils is not recommended.
- Massage of extremities which are affected by deep vein thrombosis should be avoided; the same applies for areas which may have lymphedema or are swollen.

Cancer patients often suffer from adjustment disorders, anxiety and depression, but unfortunately an adequate therapy for this kind of distress often remains unimplemented. [21]

Fatigue is also a common symptom in patients with cancer and is nearly universal in those undergoing cytotoxic chemotherapy, radiation therapy, bone marrow transplantation, or treatment with biologic response modifiers. It has a

negative effect on patients' quality of life. Patients are not able to continue their routine activities. Studies proved that corticosteroids and psychostimulants decreased fatigue in advanced cancer patients, but further investigations regarding long-term efficacy and safety are necessary. [22] [23] Recommended measures are exercise, nutrition, sleep therapy and restorative therapy.

Kohara et al. conducted a study in Japan to evaluate the positive effect of a combined modality therapy in twenty terminally ill cancer patients. It consisted of foot soak in warm water containing 1 % lavender essential oil for three minutes and subsequent reflexology treatment with jojoba oil containing also 1 % lavender essential oil for 10 minutes. The results, which were measured via the cancer fatigue scale showed significant improvement after treatment. As no side effects occurred and patients had a positive attitude to continue, combined modality therapy appears to be an effective non-pharmacologic intervention in fatigue cancer patients. The improvement in physical and cognitive subscale scores lasted about 4 hours after aroma treatment. [24]
The results were not significant due to the fact that the number of the examined attendees was small. Thus further work to confirm these results is necessary. The beneficial effects of each component in these interventions should also be analysed separately.

**Gastrointestinal symptoms**

Constipation is a well-known problem in palliative care and is commonly experienced. It is a result of dietary factors, lack of physical-activity and privacy time, and medication including analgesic, opioids, cytotoxic chemotherapy, antidepressants, anti-cholinergic and anti-emetics. Besides pain and anorexia, constipation belongs to the top three most uncomfortable symptoms in advanced cancer patients. Secondary constipation is induced by pathological changes like tumour, partial intestinal obstruction, metabolic effects or spinal cord compression. [25]

The purpose of the pilot study by Lai et al. was to explore whether aroma massage could improve constipation and quality of life in advanced cancer patients. The aromatherapy group received 20 minutes of abdominal massage

for five days and experienced an improvement in bowel movement as well as an improved quality of life. Essential oils were chosen by a qualified aroma therapist after an individual assessment. These included the oils of bitter orange, rosemary, black pepper marjoram and patchouli in olive oil. Patients in the plain massage group also reported an improvement compared to the control group. Results were measured using the Constipation Assessment Scale and McGill quality of life questionnaire. [25]

In a study conducted by Gravett et al., 42 patients with breast cancer and gastrointestinal upset due to previous high-dose chemotherapy treatment and stem cell rescue were examined. The gastrointestinal problems have been persisting beyond 5 days after the end of chemotherapy. Patients were treated with aromatherapy consisting of geranium (*Pelargonium species* (Geraniaceae)), German chamomile (*Matricaria recutita* (Asteraceae)) and patchouli (*Pogostemon cablin* (Lamiacae)). No significant differences in gastrointestinal symptoms were observed between control and intervention group. [26]

**Massage**

Contra indication for massage are swelling, bumps, painful areas, high fever, venous thrombosis, skin lesion and body areas treated by radiotherapy. [27]
There is no practical evidence that massage is associated with a higher risk of spreading cancer cells in patients suffering from different forms of cancer. [28]

In 1999 Wilkinson et al. conducted a study that evaluates the effects of massage with and without essential oils on advanced cancer patients in a palliative care centre. More than 75 % of the patients suffered from tiredness, lack of energy, anxiety, depressed mood, despondency about the future, nervousness, sore muscles, difficulty concentrating, shortness of breath, and dry mouth. They examined the effect of massage and aromatherapy massage for improving the quality of life and the patients' perceptions of massage in general. 103 patients were randomly separated into two groups. The members of the aromatherapy group received a full body massage three times in three weeks with sweet almond oil as carrier with addition of *Roman chamomile*

essential oil. Patients in group 2 had the same massage with the carrier oil only. *R. chamomile*, which is obtained by steam distillation of the dried flower heads, is well known and reduces anxiety and pain. It has a warm and sweet odour and a number of positive effects. For example it acts analgesic, antiinflammatory, antiseptic, antispasmodic, carminative, digestive and diuretic. The essential components are esters of butyric acids, azulene, chamazulene and coumarin. The benefit is that the essential oil is non-toxic, non-irritating and non-sensitising. The results indicate that massage with or without essential oil additive improves the anxiety level in advanced cancer patients. The RSCL (Rotterdam Symptom Checklist) subscales from the aromatherapy group showed a significantly higher improvement in the physical and psychological symptoms than the massage group. RSCL is a method to measure the quality of life in cancer patients. Its scale contains 39 items, including psychological disorders, physical status, functional status and overall quality of life. The STAI (State Anxiety Inventory) showed a significant reduction in anxiety after each massage. Patients felt comfortable and accepted the massage as a complementary therapy in palliative care. [29] There are negative aspects to be mentioned: The number of participants examined was too low and no control group existed. Furthermore, the information for how long the reduction of anxiety is maintained is missing.

Eight years later, Wilkinson et al. carried out a similar study to compare the effectiveness of additional aroma therapy with the usual supportive care in management of depression and anxiety. It was a large, multicentre and randomised trial with two arms. Most of the 288 participants were women and more than half of those suffered from breast cancer. All patients had access to psychological support. The aromatherapy group received weekly one hour sessions for 4 weeks in addition. 10 weeks after randomisation, depression and anxiety in the aromatherapy group was the same compared to usual care, but there was a statistically positive difference in favour of aromatherapy after a shorter term of 6 weeks. Patients also described an improvement in self-reported anxiety. The conclusion was drawn that aromatherapy massage do not benefit in the long-term but has great effects up to two weeks after treatment.

Twenty various essential oils were used, unfortunately they were not specified in detail. Hence no statement about the active agents could be given. [30]

Hadfield et al. examined whether aromatherapy massage with lavender or chamomile lead to a reduction of anxiety in eight malignant brain tumour patients after radiotherapy. "*Physical parameters, the completion of Hospital Anxiety and Depression Scales (HADS) and semi-structured interviews"* were used for analysis. Results showed no reduction in anxiety or depression, but there was a statistically significant reduction in physical parameters. They concluded that aromatherapy influences the autonomic nervous system, inducing relaxation. During interview, patients indicated that they felt relaxed after aromatherapy massage. Although the treatment options for these cancer patients are limited, the described intervention seems to be a good option to enhance the well-being. [31]

The research team of Imanishi investigated the anxiolytic effects of aromatherapy massage with essential oils of *Citrus aurantium* (Rutaceae), *Lavandula angustifolia* (Lamiacaee) and *Santalum album* (Santalaceae) in jojoba oil as carrier. 12 cancer patients received a 30 minute massage twice a week over a period of 4 weeks. Psychological parameters were measured using the STAI test, HADS and Profile of Mood State (POMS) one month before and one month after the treatment as well as during intervention. The findings revealed that aromatherapy massage reduced anxiety levels already after the first 30 minutes session. The effect persists after 8 aromatherapy massage sessions. [32]

The study of Wilcock et al. was randomised controlled and examined the effect of "*adjunctive aromatherapy massage on mood, quality of life and physical symptoms"* in 46 cancer patients attending a palliative care day centre. The recruited patients were randomly assigned to normal day care or day care plus weekly aroma massage. They received massage to the back, neck, shoulders or hands for half an hour using 1 % lavender and chamomile oils in sweet almond oil. The total duration of the therapy was four weeks. There was no significant difference between the outcomes of the two groups. However, all

patients enjoyed the therapy and there was an improvement in mood, quality of life and physical symptoms in both groups. It is worth noting that in the control group more patients were taking antidepressants compared to the aromatherapy group. The main critical issue in palliative care studies is the high attrition rate. Only 11 of 23 patients in the aromatherapy group completed the whole study compared to 18 of 23 in control group. [33]

Serfaty et al. published a randomised pilot study called ToT (Touch or Talk) to assess clinical effectivity of aromatherapy massage compared to cognitive behaviour therapy. The study was conducted over two years in cancer and palliative care patients. Attendants in aromatherapy group received standardised massage with a choice of 20 essential oils. They were screened by using HADS. It turned out that both therapy methods significantly improved POMS. The cognitive behaviour therapy performed slightly better but this outcome was non-significant. Unfortunately there is a lack of information about which essential oils were applied. [21]

Chang (2008) assessed the effect of aroma hand massage with a 1.5 % aroma blend of bergamot, lavender and frankincense in almond oil. Out of the 58 hospice patients suffering from terminal cancer 28 received aroma hand massage for five minutes on each hand for one week. The remaining 30 patients were selected as control group and got massages with plain carrier oil. Results showed a higher difference in pain score and depression at aroma group compared to control. The author concluded that terminal cancer patients benefit from aroma hand treatment. [34]

In 2004 Soden highlighted the positive influence of aromatherapy massage with lavender on physical and psychological symptoms in patients with terminal cancer. The study was placebo-controlled. No significant differences were found between the two groups. The sleep of the probands improved in both groups, depression was reduced only in the control group. [35]

Louis et al. examined whether humidified inhalation of 3 % essential lavender oil of *L. angustifolia* has an impact on vital signs, pain level, anxiety, depression

and well-being of 17 hospice patients suffering from cancer. The results were measured before and after a 60 minute treatment with aromatherapy or water humidification as control, using 11-points verbal analogues. A third group which remained untreated also served as control. The findings indicated that aromatherapy has a positive effect on blood pressure and pulse, pain, anxiety, depression and sense of well-being. Patients who received humidified water treatment achieved equivalent results. In the control group there also was a small improvement in blood pressure, pulse, depression and well-being, but not on anxiety levels or pain. [36]

The similarity between the two groups can maybe be explained by the Hawthorne effect which is based on the following definition:
"*The Hawthorne effect is a term referring to the tendency of some people to work harder and perform better when they are participants in an experiment. Individuals may change their behaviour due to the attention they are receiving from researchers rather than because of any manipulation of independent variables*." [37]
It could also be argued that steam inhalation itself shows relaxing effects.

Corner et al. (1995) measured the responses of cancer patients to back massage and aromatherapy with essential oil mix of 2% lavender, rosewood, lemon, rose and valerian to well-being in an eight-week trial. It was reported that aromatherapy massage reduces both, the anxiety as well as pain and improves the mobility. [38] Graham et al. was unable to establish a beneficial effect of inhaling lavender, bergamot and cedar wood essential oil on anxiety or depression in patients who were undergoing chemotherapy. [39]

Boehm et al. provided a systemic overview of aromatherapy as a complementary treatment in cancer patients based on literature until October 2010. They concluded that there is no long-lasting effect of aromatherapy massage. Nonetheless, in short term up to 8 weeks after treatment, good results were reported for anxiety, depression and overall wellbeing. For terms up to 2 weeks after attendance, sleep and pain control improved as well. There was a good compatibility with rare side effects including local skin irritation,

allergic contact dermatitis and some oils showed even a photo toxicity from reaction with sunlight. [1]

Den et al. performed an experimental study in 122 patients on intensive care unit. They were divided into the three groups: massage, aromatherapy with lavender or period of rest. The physiological stress and anxiety levels were measured before and after the interventions. They noticed no difference between the intervention types with respect to stress indicators or their behaviour. But patients who were receiving aromatherapy reported significantly greater improvements *"in their mood and perceived levels of anxiety".* Directly after the treatment they also felt more positive and less anxious. [40]

**Nausea**

A case study by Gilligan et al. explored the use of aromatherapy containing *Foeniculum vulgare var dulce* (Apiaceae), *Pimpinella anisum* (Apiaceae), *Anthemis nobilis* (Asteraceae) and *Mentha x piperita* (Lamiaceae) in 25 patients who suffered from nausea in a hospice and palliative care program. Most patients who received aromatherapy reported relief. But it should be noted that all patients in this trial were also using other preparations for symptom relief. Hence it is not possible to reason a clear scientific link between the treatment with essential oils and nausea relief. But nevertheless the study gave an indication that aromatherapy seems to be a valuable complement in nausea palliation. [41]

A single-blind, randomised, cross-over and controlled study by Lua et al. also dealt with the positive effects of inhaling essential oil of ginger against nausea and vomiting caused by chemotherapy in 60 women suffering from breast cancer. Patients inhaled either ginger essential oil or ginger fragrance oil as placebo for five days. The results showed significant lower VAS nausea scores in the essential oil group during acute phase. This effect didn't continue in overall treatment. Even though the essential oil had no significant influence on vomiting, a positive change in global health status from baseline as well as an improvement in appetite and on role functioning could be detected. [42]

Anderson et al. examined whether inhalation of isopropyl alcohol, peppermint oil or saline as placebo has an influence on nausea in 33 ambulatory surgery patients at post-anesthesia care unit. The severity of nausea was measured two and five minutes after intervention using a 100 mm VAS. After two minutes, the nausea scores decreased from 60.6 ± 4.3mm to 43.1 ± 4.9 mm and after five minutes to 28.0 ±4.6 mm. There was no difference in the scores between placebo and control at any time. The authors concluded that the beneficial effects are primarily explained by a controlled breathing pattern rather than the aromatherapy itself. [43]

Another randomised, placebo-controlled study by Hunt et al. focused on the effects of either inhaling ginger essential oil, a blend containing ginger, spearmint, peppermint, and cardamom essential oil, ginger essential oil alone or isopropyl alcohol on postoperative nausea. Patients rated their nausea level on a verbal descriptive scale ranging from 0 to 3, before and after deep inhaling of the volatile substances three times. The results showed a significant change in nausea levels when using ginger compared with saline, which acted as placebo. Patients needed less antiemetics after aromatherapy with both ginger and essential oil blend compared to saline. [44]

Tavarani-Najaran et al. investigated the essential oil from *Mentha spicata* (Lamiaceae) and *M. x piperita* for its antiemetic properties in chemotherapy induced vomiting and nausea. The study design was randomised, double blind and placebo controlled. The control group proceeded with their common antiemetic therapy. In the first 24 hours after application both essential oils exhibited a significant decrease in the number of emetic events and their intensity. As there were no side actions reported, the volatile oil of *M. x piperita* and *M. spicata* represent a safe and effective alternative. [45]

**Examples for implementation in palliative care units**

Berger et al. reported about the development of providing complementary treatments at a palliative care unit in a hospital located in Ontario. This pilot project included the interdisciplinary therapies massage, aromatherapy, Reiki,

and Therapeutic Touch™. The results showed a significant improvement of pain, anxiety, low mood, restlessness, discomfort, inner stillness and peace.
The following aromatherapy products were used:

- Aromatherapy massage oil
- Mouth care products against dry mouth or lips, malodour or pain in the mouth
- Aromatherapy ointment for red, inflamed or painful intact skin
- Aromatherapy moisturizing cream for dry or itchy skin
- Aromastick inhaler for breathlessness or anxiety

[46]

The Neill Cliffe Cancer Center located in the United Kingdom, offers patients and carers support at any time – from the diagnosis, treatment phase, and palliative care, throughout the terminal phase. Aromatherapy is one of the available complementary methods. In aromatherapy and relaxation group, patients are offered hand or foot massage, followed by an optional relaxation session in a small group. Patients then have the opportunity to contact other patients with similar diseases. Patients also have the possibility to receive aromatherapy on a one to one basis, as well as a combination of aromatherapy and physiotherapy to restore functions of restricted movements. Patients nearing the end of their therapy programmes, are taught the massage techniques and safe ways of using essential oils on their own to continue the treatment at home. [18]

# 3 Pain therapy

Many people throughout the world suffer from some kind of pain. Pain is caused by mechanic, thermic or chemical noxious agents. The International Association for the Study of Pain (IASP) defines pain as, *"an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"*. [47] Tissue damage leads to the release of different substances such as $K^+$, $H^+$, serotonin, histamine, substance P, acetylcholine or bradykinin. These substances stimulate nociceptors. Furthermore, products from arachidonic acid metabolism, like prostaglandins, are involved in inflammatory events. They do not cause pain themselves but enhance the nociceptive effect of other pain triggers. A distinction is made between chronic and acute pain. Acute pain occurs posttraumatically and postoperatively. Chronic pain is associated with many diseases including cancer, rheumatoid arthritis, diabetes, multiple sclerosis or herniated disks. [48]
In general, essential oils could help to ease several types of pain and therefore the oils are successfully applied in pain therapy. The primary action mechanisms of essential oil prescriptions against pain are a reduction of inflammation and spasm, by acting as counter-irritants in causing hyperaemia, by disrupting *"the pain impulse at the spinal or supraspinal level*" and by "*peripheral mechanisms that inhibit the influx of nociceptive impulse*". [2]

**Counter irritants**

Counter-irritation is defined as *"an irritation or mild inflammation produced to relieve inflammation of underlying or adjacent tissues"*. [49]
Among the most common counter irritants are clove bud, cinnamon leaf, eucalyptus, wintergreen, camphor, laurel, juniper, lavender, pine and spruce needle. The exterior application of these oils and preparations lead to a local irritation. The provoked effect may be effective to relief rheumatic and neuralgic discomfort. [5]

**Headache**

Many people are affected by headaches. A reduced quality of life, high societal costs and lost work-place-productivity are the consequences. Primary headache is the most commonly self-treated disease and a lot of painkillers are sold to

treat it. This in turn can cause problems, such as drug-induced headache and severe liver and kidney intoxications. Therefore, it is becoming increasingly important to search for soft alternatives to relief headache pain. [50]

Peppermint oil with its main constituents menthol, menthylacetate, menthone, isomenthone and cineole is a frequently used phytopharmaceutical. It is used for numerous of indications, such as spasmodic complaints of the digestive system, dyspepsia and muscle pain, orally administered in the form of tea preparations, capsules and liquid formulations or externally applied in the form of creams or bath additives. It is extracted from leaves of *M. x piperita*. The local application of peppermint oil creates a cooling effect on skin by means of an interaction of menthol with TRP (transient receptor potential channel) receptors. This causes an anaesthetic effect. [5]
When treating infants with menthol, particular caution should be exercised, to minimise the risk of apnoea, cyanosis, and respiratory arrest. [51]

Göbel et al. compared the effectiveness of locally applied peppermint oil with acetaminophen (= paracetamol) in a double-blind, placebo-controlled, randomised, crossover study with 41 patients suffering from tension-type headache. An attack was treated by two orally administered doses of acetaminophen 500 mg or placebo and an application of oil preparation (peppermint oil 10% in ethanol or placebo with traces of peppermint for blinding) onto the forehead and temples. Patients kept a headache diary and headache parameters were documented every 15 to 60 minutes. Patients treated with peppermint oil reported a significant reduction of headache intensity after 15 minutes already. There was no significant difference to acetaminophen. However, an additive effect of the two substances at simultaneous application could be observed. Peppermint oil was well tolerated and no adverse effects were reported. [52] This author group also showed that eucalyptus oil preparations had only little influence on pain sensitivity compared to peppermint. [53]

The effect of inhaling Lavender essential oil in treatment of migraine headache was observed in a placebo-controlled clinical trial by Sasannejad et al. [54]

47 patients with diagnosis of migraine headache were randomly divided into control and lavender group. Lavender group inhaled essential oil and control group liquid paraffin for 15 minutes. Patients recorded their headache symptoms. Half of the patients responded partially or entirely positive to lavender. There was a statistically significant difference in responding in favour of the lavender group. [54] Galeotti et al. found out that orally administered (-)-menthol selectively activates central κ-opioid receptors. Involvement of δ-receptors could be excluded because an administration of the δ-antagonists 7-benzylidenenal-trexone and naltriben did not prevent an anti-nociception. (+)-menthol did not show analgesic effects. [55]

**Clove oil / Eugenol**

Clove oil is obtained from dried flower buds of the evergreen clove tree *Syzygium aromaticum* (Myrtaceae). Main constituents of clove oil are eugenol with a content of 75-88 %, aceteugenol and β-caryophyllene. Clove oil and isolated eugenol are used in dentistry as a canal filling material supplement and as a local anaesthetic, but the use becomes increasingly unimportant. In practise it is used in mouthwash against pharyngitis and inflammation of the oral mucous membrane. [5] Alqareer and his colleagues studied whether clove gel can replace benzocaine as a topical anaesthetic applied to maxillary canine buccal mucosa before needle insertion in dentistry. It turned out that both substances led to significantly lower pain scores. It was measured via VAS (see figure 1) in comparison to placebo in 73 participants. [56] Unfortunately no concrete statements about eugenol concentration of clove gel were given.

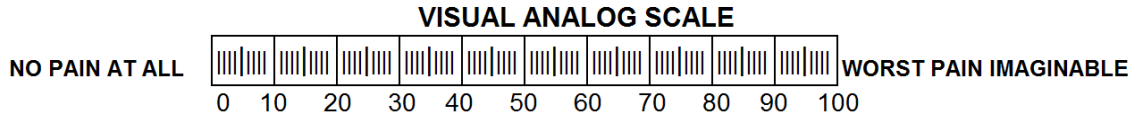


*Figure 1 - The visual analogue scale (VAS) is often used to rate the intensity of felt pain. (newly drawn from Hospice Education Institute [57])*

In 1990, Jorkjend and Skoglund compared non-eugenol and eugenol-containing periodontal dressings against postoperative pain after periodontal surgery in a randomised study. All patients were pretreated with the local anaesthetic

lidocaine and adrenalin. Results showed that participants receiving eugenol-free dressings reported greater pain in the first 12 hours after surgery. The researchers suggested that these results may be due to local anaesthetic effects of eugenol on nerve fibres. [58] Lee et al. revealed that eugenol inhibits high-voltage activated calcium channels both in capsaicin-sensitive and capsaicin-insensitive dental primary afferent neurons. This effect was not blocked by transient receptor potential vanilloid 1 (TRPV1) antagonist capsazepine. [59] One year later the same group found out that eugenol inhibits two types of voltage-gated sodium channels - tetrodotoxin-resistant and tetrodotoxin-sensitive. The tests were performed on dental primary afferent neurons of rats using the patch-clamp technique. The pre-treatment with capsazepine was also not able to block the inhibition. [60]

**Methyl salicylate**

Methyl salicylate is the major component of wintergreen oil and is naturally found as glycoside in *Gaultheria procumbens* (Ericaceae) and *Betula lenta* (Betulaceae). Nowadays it is synthetically produced. [5] In the skin methyl salicylate is transformed into salicylate. This was revealed by Behrendt and Kampffmeyer, who investigated the absorption in rabbit ears. [61] Higashi et al. assessed the safety and efficacy of patches containing 10 % methyl salicylate and 3 % l-menthol in adult patients with muscle strain and found out that a single 8 hour application led to significant pain relief compared to placebo. No notable adverse effects were observed. These patches were approved by FDA for patients suffering from mild to moderate pain due to arthritis, backache, strains or bruises. [62]

A research by Morra et al. concluded that transdermal application of methyl salicylate 12.5 % led to a salicylate serum concentration between 0.31 and 0.91 mg/l within one hour after application. Multiple applications may increase the absorption. [63] Other clinical trials also demonstrated a systemic absorption. [64] Orally administered methyl salicylate is accompanied by unpleasant toxic side effects and is obsolete. [65] In young children and infants methyl salicylate administration could trigger life-threatening situations. Severe allergic reactions can be the result. [66] Due to the high systemic salicylate concentration,

cyclooxygenase is inhibited whereby less prostaglandins are liberated from arachidonic acid. Thus acetylsalicylic acid contraindications also apply to methyl salicylate. Scientists also reported a potentiation of Warfarin with methyl salicylate. [67]

**Local anaesthesia**

As already mentioned above, eugenol has effective local anaesthetic properties. Dolara et al. examined the local anaesthetic properties of the sesquiterpenes obtained from *Commiphora molmol* (Burseraceae). These included furanodiene-6-one and methoxyfuranoguaia-9-ene-8-one. They found out that the local anaesthetic effect is caused by a block of inward sodium currents in mammalian excitable membranes. [68]

**Carpal tunnel syndrome**

In 2014, Sundstrup et al. published that topically applied menthol to hand and wrist reduces pain in ten carpal tunnel patients compared to placebo. They considered that menthol represents an effective non-systemic alternative to regular analgesics in treatment of chronic and neuropathic pain. The fact that these results were assessed only in subjective rating scales is a limitation of this study. [69]

**Multiple sclerosis**

Beside other distress symptoms like fatigue, bowel and bladder problems, and visual disturbances, a large number of multiple sclerosis patients suffer from pain. Additional to acute pain, which includes optic neuritis and trigeminal neuralgia, chronic pain, such as dysesthesia, pain in a joint or other musculoskeletal problems may occur. The source of the pain may result from the neuronal damage or muscular-skeletal problems. Conversely, alleviating the pain may produce negative symptoms, like increased fatigue. [70]

Howarth published a paper which assessed the use of aromatherapy and massage in patients diagnosed with multiple sclerosis in the multidisciplinary pain clinic at the Royal Hallamshire Hospital in Sheffield. Patients received an aromatherapy massage on back, neck, legs or arms each of four consecutive

months. Additionally, they were given the opportunity to use the massage oil themselves at home between the monthly interventions. Even though the therapy could not rid patients of their pain, it did help to improve sleep disturbance, joint and muscle mobility and overall comfort and relaxation. [71]

**Gynaecology**

The options for conventional treatment of women during pregnancy, birth, or lactation period are limited. Also pain relief after caesarean constitutes a big challenge. Many drugs could cause serious damage to the unborn child or to the new-born when substances are excreted through the breast milk. Many studies had been conducted to investigate the positive effects of essential oils on women's health.

Dysmenorrhea, which is classified into primary and secondary dysmenorrhea, is one of the most common gynaecologic disorders affecting many menstruating women. Lower abdominal cramps are the most common symptom and very unpleasant. The felt pelvic pain - which is believed as the result of excessive PGF2 α release - interferes with women's daily activities. [72]

Ou et al. examined the effect of daily lower abdomen massage throughout the menstrual cycle in 48 patients suffering from primary dysmenorrhea. Patients were randomly divided into two groups. The essential oil group massaged their lower abdomen with a cream consisting of 3 % of a 2:1:1 blend of the essential oils of *Lavandula officinalis*, *Salvia sclarea* and *Origanum majorana*. The second group used a synthetic fragrance. In both groups the numeric and verbal pain rating decreased significantly after one cycle. In the essential oil group a reduction of pain duration from 2.4 to 1.8 days was observed. They identified linalyl acetate, linalool, eucalyptol and β-caryophyllene as the active analgesic compounds of the used blend. [73] Han et al. performed a randomised, placebo controlled trial. This study investigated whether abdominal aromatherapy massage with two drops of lavender (*L. officinalis*), one drop of clary sage (*S. sclarea*) and one drop of rose (*Rosa centifolia*) essential oil in 5 cc of almond oil as carrier has a positive impact on pain severity of menstrual cramps. 67 female college students were randomised into three groups:

experimental group, placebo group and control group. Placebo group received the same abdominal massage as aromatherapy group but with carrier oil only, whereas control group received no treatment. Inclusion criteria were not taking hormonal contraceptives and cramps greater than 6 on a 10-point VAS. Results reflected a significant decrease in severity of dysmenorrhea symptoms in the aromatherapy group. [74] Dehkordi et al. demonstrated the positive effect of inhaling essential oil of *L. angustifolia* "*on the symptoms of primary dysmenorrhea and the amount of menstrual bleeding*" by performing a randomised clinical trial. 96 female students were followed up during four menstrual cycles. Conditions were that they suffer from level two or three of dysmenorrhea, having regular cycles, taking no contraceptives and having no genital organs disorders. Symptoms significantly decreased in the aromatherapy group compared to control group. The amount of bleeding was reduced as well, but not statistically significant. [75]

In a prospective randomised cross-over study performed by Marzouk et al., *"the effect of aromatherapy abdominal massage on alleviating menstrual pain"* was examined. A total of 95 students were randomly assigned into two groups. In the first treatment phase the aromatherapy group received a daily ten-minute abdominal massage for one week prior to the beginning of the bleeding, using a 5 % blend of cinnamon, clove, rose and lavender in almond oil. Control group received the same massage with the carrier almond oil only. In the second phase, the treatment was switched between the two groups. The results showed that both *"the level and duration of menstrual pain"* and intensity of bleeding decreased significantly in the aromatherapy group compared to placebo. [76] These studies suggest that treatment with essential oils represents a good alternative therapy for women suffering from dysmenorrhea.

Breastfeeding mothers often suffer from nipple pain and damage. Numerous women stop breastfeeding before they wanted or planned to do so due to these distress symptoms. The performed studies cited below suggest that peppermint formulations, along with good breastfeeding techniques, are a very helpful option to prevent painful nipple cracks. In 2007, Sayyah et al. examined the effectiveness of the application of peppermint water versus expressed breast

milk in 196 breastfeeding mothers. The tested women were followed up for three times within two weeks and after six weeks postpartum. Patients using expressed mother milk (27 %) more often reported from cracked nipples and areolas compared to peppermint water (9 %). The felt nipple pain was also less pronounced in the peppermint group. [77]

In the same year, Melli et al. performed a randomised double-blinded study to evaluate the effect of the three formulations peppermint gel, modified lanolin and neutral ointment (as placebo) on 216 breastfeeding women. Each participant applied one of the formulations on both breasts for two weeks. Here, too, better results were noticed in the peppermint group than in the other groups. [78] A more recent study performed in 2014 by Akbari et al., confirmed the considerably positive effects of peppermint essence in comparison to the application of expressed breastmilk in improving nipple fissures. 55 women were observed for 14 days. [79]

The process of giving birth is always associated with pain. To alleviate this pain, pharmacological and non-pharmacological methods are applied. Pharmacological measurements include systemic medication, inhalational, topical and general anaesthesia, whereas light therapy, reflexology, massage, acupuncture and aromatherapy are non-pharmacological approaches.

Namazi et al. investigated the analgesic effect of *C. aurantium* in 126 women aged between 18 and 35 years, who gave birth to their first child. Patients were randomly assigned to an intervention group and a control group. In the intervention group, wipes were soaked in *C. aurantium* distilled water and in normal saline in the control group. The wipes were placed on the women's collar. As seen in the table below, pain scores reduced at 3-4 cm, 5-7 cm and 8-10 cm cervix dilatations for women in the aromatherapy group compared to control. [80]

| Dilatation stages in labour | Aromatherapy group: mean and standard deviation | Control group: mean and standard deviation | Result of the independent t-test |
|---|---|---|---|
| before intervention | 7.38 ± 0.888 | 7.52 ± 0.948 | p=0.384 |
| 3-4 cm dilatation | 4.97 ± 0.740 | 8.08 ± 0.679 | p<0.001 |
| 5-7 cm dilatation | 6.65 ± 0.481 | 8.67 ± 0.568 | p<0.001 |
| 8-10 cm dilatation | 7.57 ± 0.560 | 9.46 ± 0.534 | p<0.001 |

*Table 1 - This table shows the average pain scores and standard deviations of primiparae in the different cervical dilations according to study groups. (Newly drawn according to Namazi et al. [80] )*

Olapour et al. assessed the impact of inhaled lavender essential oil on caesarean postoperative pain in a triple blind, randomised placebo-controlled trial. 60 pregnant women with planned caesarean section were randomly divided into two groups. Pregnant women with ASA (American Society of Anesthesiologists) class larger than two, hypertension, disturbance of blood coagulation, migraines and chronic headaches, allergies to medical plants and anosmia were not included. Also patients *"with respiratory problems during surgery, nausea, vomiting"*, and displeasure after the first dose of inhalation were ruled out. Once the postoperative pain after caesarean section began, the lavender group inhaled three drops of 10 % *L. angustifolia* oil essential oil and the placebo group inhaled three drops of placebo for five minutes after four, eight and twelve hours. Before and after the intervention, the perceived pain was measured using a VAS. The vital signs, complication and level of satisfaction were recorded as well. Both groups requested analgesics after the same amount of time. Nevertheless, there was a significant decrease in pain levels at lavender group compared to placebo at four, eight and twelve hours after the symptoms appeared. The decrease of the heart rate, as well as the increase in patient's satisfaction with analgesia were also greater in the essential oil group. Patients in the placebo group required diclofenac suppositories more frequently. A multi modal pain therapy seems necessary after caesarean section. Lavender inhalation *"is not recommended as the sole pain management."* [81]

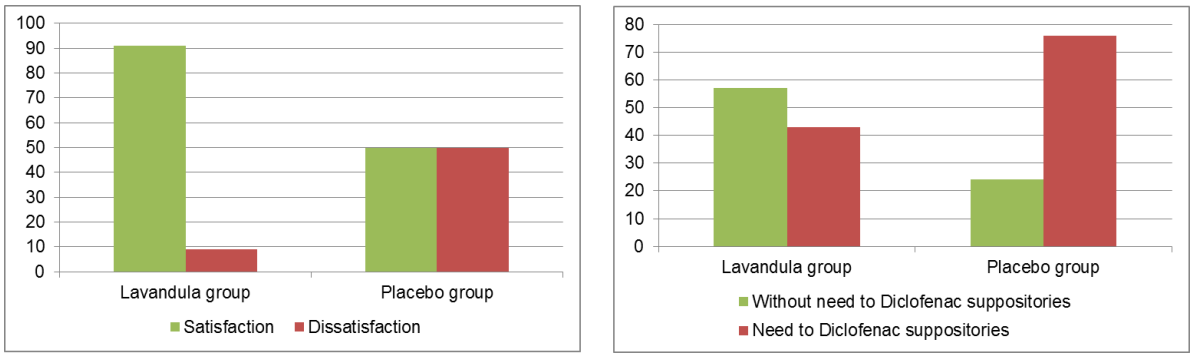


*Figure 2 - The figure demonstrates the satisfaction (%) with the therapy and the frequency (%) of patients need to take additional diclofenac suppository for analgesia. (newly drawn according to Olapour et al. [81])*

Hadi et al. performed a similar study and examined 200 women after caesarean section. Three hours after administration of intravenous analgesics, they received lavender essential oil or similar aromatic material as control for 3 minutes using an oxygen mask. At baseline, VAS did not differ between the groups. After the first intervention, VAS decreased in both groups but was more significant in the aroma group after half an hour, 8 and 16 hours after first intervention. [82] In April 2015, Metawie et al. also confirmed that inhalation of lavender oil led to a significant decrease in pain intensity compared to placebo. His working group observed 100 post caesarean patients between October 2013 and January 2014. The inhalation was also performed for 3 minutes via an oxygen facemask. [83]

In a recently published study by Kaviani et al. [84] 156 primiparous women in labour were assessed regarding pain intensity and the duration of the first and second stages of labour. They were divided into salvia, jasmine and control group. The salvia group inhaled 3 ml essential oil of *Salvia officinalis* (Lamiaceae) and the jasmine group 3 ml essential oil of *Jasminum officinale* (Oleacae). Both oils were diluted in 5 ml of water and inhaled using an incense mask. Qualitative measurements with gas chromatography were performed and analysis showed that the essential oil of salvia was rich of camphor, whereas no effective compound was found in jasmine. The control group inhaled distilled water only. The severity of pain was measured using the VAS before, as well as 30 and 60 minutes after intervention. The results showed a significant reduction in pain severity and duration of the first and second labour stages in the salvia

group 30 min after treatment. After 60 minutes, no significant differences between the three groups were measureable. (see table 2) Furthermore, no negative impact on the new-born child was detected using first- and fifth-minute APGAR scores. [84] APGAR stands for Appearance, Pulse, Grimace, Activity and Respiration and is used to determine the clinical condition of the new-born. [85]

| | Jasmine | | Salvia | | Control | | P value |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | |
| **Before the intervention** | 4.35 | 0.86 | 4.13 | 0.84 | 4.19 | 1.1 | 0.5 |
| **30 minutes after the intervention** | 3.19 | 1.1 | 2.46 | 0.87 | 3.17 | 1.2 | 0.001 |
| **60 minutes after the intervention** | 4.31 | 0.9 | 4 | 0.84 | 3.98 | 1.27 | 0.1 |

*Table 2 - The table shows the mean VAS and standard deviations before, 30 and 60 minutes after the treatment in primiparous women with cervical dilation of 3-4 cm. (newly drawn according to Kaviani et al. [84])*

In a large scale study for 8 years the effects of aromatherapy on reduction of labour pain, anxiety and fear of 8058 women in childbirth were investigated by Burns et al. Ten different essential oils were used and administered via skin absorption and inhalation. 60 % experienced a relief of their pain by clary sage oil and chamomile oil and reduced anxiety and fear by lavender oil and frankincense. Only 1 % of the treated women reported adverse effects. [86] In 2007, Burns and his colleagues also published a prospective trial with two treatment options comparing aromatherapy with standard care. *L. angustifolia* (Lamiaceae), *Citrus reticulate* (Rutaceae), *Chamaemelum nobile* (Asteraceae), *Boswellia carteri* (Burseraceae) or *Salvia sclarea* (Lamiaceae) were used of 251 women out of 513. Sweet almond oil was used as carrier for the essential oils. The rate of needing a caesarean section, ventouse, Kristeller manoeuvre (a practice of pressing on the uterine fundus to promote a vaginal birth), first-stage augmentation and second-stage augmentation did not differ between the groups. The vaginal birth proportion was the same in both groups. It is noteworthy that primiparae experienced less pain in aromatherapy group. [87]

**Back pain**

Sritoomma and his colleague's examined the effect of Swedish massage with aromatic ginger oil in patients aged 60 years and older with chronic low back pain compared to traditional Thai massage. [88] The randomised controlled study was conducted in a massage clinic in Thailand. 140 patients were separated into two randomised groups. Twice a week, they received either a Swedish massage with aromatic ginger oil or a traditional Thai massage for 30 minutes. Swedish massage is a superficial massage technique consisting of five main stroking actions which stimulate the blood circulation through the soft tissues. Thai massage is classified as a deep tissue massage with acupressure which follows two meridians energy-lines on the back. After each massage, a measurement using VAS was made and a short McGill Pain Questionnaire had to be filled in to measure the short-term (six weeks) and long-term (15-weeks) effectiveness. Both massages reduced the intensity of pain, but the application of aromatic ginger oil was more effective. [88] The analgesic effect of ginger essential oil has already been described in other studies.

**Knee pain**

Yip and Tam performed an experimental, double-blind and placebo-controlled study to investigate the effectiveness of massage with essential oils of *Zingiber officinale* (Zingiberaceae) (1 %) and *Citrus sinesis* (Rutaceae) (0.5 %) against moderate to severe knee pain in 59 elderly persons. They received six massages over a period of three weeks. Significant changes in knee pain intensity and stiffness levels between baseline and after the first and fourth week of intervention were observed. Changes in physical function and pain were superior in the intervention group compared to both placebo and control group after the first week. These effects, however could not be sustained after four weeks. Measuring the changes in quality of life, no statistical difference between the three groups was registered. [89]

**Shoulder Pain**

Byung-Cheul and Myeong compared the positive effect of aromatherapy acupressure compared to acupressure alone in 30 stroke patients suffering from hemiplegic shoulder pain. The additional aromatherapy with the essential

oils of lavender, rosemary and peppermint performed significantly better than acupressure alone at post-treatment. The treatment was performed twice a day for 14 days. In addition, they found out that motoric strength significantly improved post-treatment in both groups, but there was no difference between the two groups. [90]

**Postoperative pain**

In a pilot study conducted by Kim et al., the analgesic efficacy of essential lavender oil on postoperative pain after breast biopsy surgery was tested. Half of the 50 patients received oxygen with drops of 2 % lavender oil via a face mask postoperatively. The control group received the same intervention but without the essential oil. Intensity of pain was measured with a numeric rating scale at 5, 30 and 60 minutes after arriving in the post-anaesthesia care unit. Also, the narcotic use, the incidence of nausea or vomiting, the satisfaction with pain control and stay time in recovery room were documented. They noted no significant differences between the groups except a higher overall satisfaction rate with pain control in lavender group. [91] These findings appear to be consistent with another study carried out by Gedney et al., who described that aromatherapy decreases the subjective experience of pain-discomfort but does not exert a verifiable analgesic effect. [92] Marofi et al. analysed the essential oil of *Rosa damascene Mill.* and its effect on postoperative pain in 64 children at the age of 3 to 6 years. Half of the patients received inhalation with the essential oil, whereas the rest were given almond oil as placebo. Common pain relievers have been additionally administered to both groups. 30 minutes after intervention the felt pain was evaluated using the Toddler-Preschooler Postoperative Pain Scale (TPPPS). A decrease in pain intensity was measured in both groups, but the effect was stronger in aromatherapy group. [93]

In 2013, Soltani et al. carried out a study to test the effectiveness of *L. angustifolia* essential oil in paediatric patients after tonsillectomy. [94] The 48 participating children were aged between 6 and 12 years. Patients were randomly divided into two groups. After surgery, all patients received acetaminophen every six hours to relieve pain, if needed. The case group also inhaled lavender essential oil. The waking up at night, the pain intensity as well

as the frequency of acetaminophen use were recorded for three days. Pain intensity was measured using the VAS. Patients receiving lavender oil inhalation required significant less of acetaminophen on all postoperative days compared to control group. But there was no significant effect on nocturnal awakening or pain intensity. [94]

In a clinical single-blind study of Salamiti et al. [95], the effect of inhalative *L. officinalis* essential oil in 40 patients undergoing open-heart surgery was observed. The precondition was that the candidates should not take opioids within two hours before extubation. The oil was applied at a concentration of 2 % via a cotton swab in the oxygen mask. Pain intensity after this intervention was compared to the intensity before treatment using VAS. No significant differences were found. The research showed that the inhalation of the oil does not have the potential to reduce the pain. [95]

**Haemodialysis**

Ghods et al. performed an open crossover study in 34 haemodialysis patients to assess whether the topical application of essential oil of lavender has a positive influence on the pain intensity when inserting the dialysis needles. Patients were divided into the three groups: essential oil, no intervention and water as placebo. Pain intensity was measured using a numeric rating scale. The intensity was 2.91 ± 1.69 in intervention group, 4.59 ± 2.02 at no intervention and 4.18 ± 1.66 at placebo group. These findings suggested that lavender essential oil has a positive effect for this indication. [96]

Bagheri - Nesami et al. were able to confirm the pain relieving effect of inhaled lavender essential oil (concentration of 10 %) "*on pain following needle insertion into a fistula in haemodialysis patients*". [97] 92 patients were randomly divided into an experimental and a control group. The intervention was applied for five minutes during three haemodialysis sessions. The VAS pain score was 3.78 ± 0.24 in the intervention group and 4.16 ± 0.32 in the control group before the treatments. After three sessions, VAS score was 2.36 ± 0.25 and 3.43 ± 0.31 which indicates that lavender essential oil may be effective to provide pain relief. [97]

**Neck pain**

A randomised, controlled study by Ou et al. [98] analysed the improvement in neck pain intensity when using a 3 % cream of essential oils from marjoram, black pepper, lavender and peppermint at the ratio of 2:2:1:1. The major constituents of the used essential oils were (-)-4-terpineol (10.5 %) and trans-sabinene hydrate (7.3 %) (marjoram), caryophyllene (16.7 %) and D-limonene (15 %) (black pepper), linalyl acetate (28.9 %) and linalool (25.2 %) (lavender) and menthol (34.8 %) and p-menthone (17.9 %) (peppermint).

The control group applied an unscented cream with no essential oils.

It can be summarised that the experimental group showed better results. The essential oil cream used in this study can be applied to improve neck pain. Quantification of pain intensity was measured using PPT (Pressure Pain Treshold) and MAS (Motion Analysis System). [98]

**Animal Studies**

Many studies are showing evidence for antinociceptive activity of essential oils. The antinociceptive system, which is part of the central nervous system, has the function to extenuate forwarding of pain impulses, which results in a reduction of pain. Nociceptors are nerve endings which respond to noxious cold and heat, high threshold mechanical stimuli and a variety of chemical mediators. [48]

To demonstrate antinociceptive properties of essential oils, animal experiments were performed. The pain was triggered experimentally.

The following methods can be used:

- Acetic acid - induced writhing test
- Formalin test
- Tail flick test
- Hot-plate test
- Carrageenan edema test
- Dextran edema test
- PBQ-induced abdominal constriction test

In the writhing test an irritant, *„ including phenylbenzoquinone, acetylcholine, dilute hydrochloric or acetic acid, or bradykinin "*is intraperitoneally injected. This results in an irritation of *"serous membranes of the peritoneal cavity and evoke abdominal contractions, body movements, asymmetric contraction of dorsal abdominal muscles, and reduced locomotion"*. The assay represents a model for visceral pain but also activates somatic afferents. [99] The acetic acid - induced writhing method is a test model for evaluation of peripheral antinociceptive activity. [100] It was published that acetic acid acts indirectly by inducing the release of PGE2, PGF2 α and lipoxygenase products. [101]
In the hot plate test the rodents *"are placed on a heated plate and latencies for paw licking and jumping responses"* are noted. These ways of behavior *"are mediated through a combination of spinal and brainstem processes"*.
In tail flick test radiant heat is applied *„to a localised tail region or immersion in prehated water"*. The response to the tail flick test *"is known to be a spinal reflex"*. [99]

Popović and his working group studied antinociceptive and antiedematous properties of the essential oil extracted from the underground parts of two Laserpitium species (*Laserpitium ochridanum* and *L.zernyi* (Apiaceae)*)*, which are endemic in the Balkan. Main compounds of *L. ochridanum* essential oil are α-pinene (33.2 %), α-bisabolol (10.3 %) and chamazulene (14.9 %). *L. zernyi* essential oil consists of α-pinene (33.2 %) and α-bisabolol (30.9 %). Oral pre-treatment with both oils showed a significant dose dependent antinociceptive effect in rats with localised inflammation induced by carrageenan. Doses of at least 45.9 ± 4.9 mg/kg for *L. zernyi* and 42.4 ± 2.1 mg/kg for *L. ochridanum* oil were necessary to achieve the desired effect. An anti-edamatous effect could also be observed. [102] The antinociceptive and antiinflammatory properties of the essential oil of *Eugenia candolleana DC.* (Myrtaceae) in mice were the focus of a research by Guimarães et al. The researchers showed that intraperitoneal injection of 25, 50 and 100 mg/kg was able to reduce significantly the number of writhes in the writhing test and the number of paw licks in formalin test during phase 2. The carrageenan-induced leukocyte migration was also inhibited. The reaction time in hot plate test did not change. On the basis of their observations, they concluded that the antinociceptive and

antiinflammatory effects *of E. candolleana DC.* essential oil are probably linked to an inhibition of prostaglandin synthesis or further peripheral pathways. [103] Hasanein et al. tested whether the essential oil of *Melissa officinalis* possesses antinociceptive properties in diabetic rats undergoing formalin test. Non diabetic rats were used as control. They found out that doses of 0.04 mg per day led to significant antinociceptive effects on diabetic hyperalgesia. This effect was less pronounced in control rats using doses of 0.02 and 0.04 mg per day. 0.01 mg per day seemed to be too low to exert any effect. [104] Further research is necessary to investigate the described positive effect on the painful diabetic neuropathy.

Recently, Maham et al. performed various experimental models on mice and rats to assess antinociception triggered by the essential oil of *Artemisia dranunculus* (Asteraceae). [105] They also identified the $LD_{50}$ dose of the essential oil as 1250 mg/kg. This suggests that it has a good safety profile. The licking time induced by sub-plantar injection of 2.5 % formalin was significantly reduced by tarragon oil in doses of 100 and 300 mg/kg in both early (0-5 min post injection) and late (between 15 and 30 minutes post injection) phases. Doses of 30 mg / kg only affected the late phase. In the hot-plate test doses of 10-300 mg/kg led to an increase in latency time which confirmed the central involvement in the analgesic profile. Also nociception triggered by acetic acid was significantly inhibited. The opioid antagonist naloxone did not antagonise the analgesic effect in the acetic acid-induced writhing test. Thus they concluded that *“mechanisms other than opioid receptors are involved in the analgesic effect*”. Morphine was used as standard substance. Acetic acid induced an increase of PGE2, PGF2α, serotonin and histamine in peritoneal fluids. The main compounds of the essential oil of *A. dranunculus* are menthol, anethole, anisole, anisic acid, d-sabinene, estragole, limonene, pulegone, myrcene, ocimene and β-pinene. [105]

The monoterpenes 1,8-cineole and β-pinene, both found in the essential oil of *Eucalyptus camaldulensis* (Myrtaceae) leaves, were evaluated for their antinociceptive properties in a study by Lipai et al. [106] Tail-flick and hot-plate method in mice and rats were used to reflect the spinal and supraspinal levels.

1,8-cineole exerted an antinociceptive effect similar to that of opioid-agonist morphine in both models of pain. There appeared to be a significant synergistic effect between morphine and 1,8-cineole, but naloxone was only able to antagonise morphine. β -pinene showed only supraspinal antinociceptive effects in rats and was able to reverse the antinociceptive effect of morphine, probably by acting as a partial agonist at μ-opioid receptors. This effect was comparable to that of naloxone. The working group also discovered a structure-activity-relation between the two pairs morphine + 1,8-cineole and naloxone + β-pinene. Similarities in the stereochemistry and atomic charges have been shown. [106]

Nogueira et al. observed the antinociceptive effect of the essential of *Croton cordiifolius* Baill. leaves (Euphorbiaceae*)* with its major components 1,8-cineole and α-phellandrene in mice. They came to the conclusion that the oil is able to exert an antinociceptive effect in a chemical model of pain, at least in part, by inhibiting the glutamatergic system. Opioid antagonist naloxone did not affect the outcome, which indicates that the opioid system isn't involved. [107] Martínez et al. found out that both the endogenous opioidergic and the serotonergic system via 5-HT1A receptors participate in the antinociceptive effect of *R. officinalis* L. essential oil. Intraperitoneal treatment with volatile oil of rosemary produced a significant reduction in dysfunction in the PIFIR model (pain-induced functional impairment model in the rat) in a dose-dependent manner, especially at higher doses. [108]

In a recent study, published in 2015 [109], Raskovic et al. also dealt with the analgesic properties of orally administered essential oil of *Rosmarinus officinalis L*. and its pharmacodynamic interactions with acetaminophen and codeine in mice by performing the hot plate test. 1,8-cineole, camphor and α-pinene were identified as the main constituents. The investigated oil significantly increased the latency time to heat-induced pain between minute 20 and 50 compared to saline-treated group. Doses of 20 mg/kg seemed to be more efficient than doses of 10mg/kg. The analgesic effect of the essential oil was slightly higher than that of acetaminophen, but significantly weaker than that of codeine, especially when considering minute 5 to 20 (see table 3).

| | 0 min | 5 min | 10 min | 15 min | 20 min | 30 min | 40 min | 50 min | 60 min |
|---|---|---|---|---|---|---|---|---|---|
| **Control group (saline)** | 10.9 ± 2.8 | 11.1 ± 2.5 | 9.9 ± 2.2 | 12.5 ± 3.4 | 10.1 ± 1.8 | 10.9 ± 2.8 | 10.3 ± 1.7 | 11.6 ± 1.6 | 11.9 ± 2.5 |
| **Essential oil (*R.officinalis*)** | 10.9 ± 2.8 | 12.9 ± 3.3 | 13.8 ± 7.7 | 15.2 ± 3.0 | 14.2 ± 3.2 | 14.7 ± 5.2 | 14.2 ± 6.5 | 15.6 ± 3.1 | 14.4 ± 3.9 |
| **Codeine** | 10.9 ± 2.8 | 20.1 ± 8.7 | 20.8 ± 12.8 | 21.1 ± 14.2 | 15.9 ± 5.1 | 13.7 ± 4.8 | 15.4 ± 5.8 | 15.7 ± 3.0 | 14.5 ± 3.9 |
| **Acetaminophen** | 10.9 ± 2.8 | 10.3 ± 1.1 | 12.4 ± 3.9 | 11.7 ± 2.3 | 11.1 ± 3.8 | 11.6 ± 2.5 | 12.4 ± 1.8 | 13.3 ± 2.3 | 12.1 ± 5.1 |

*Table 3 - The table shows the response latency time to heat-induced pain in the different groups in seconds. All data is expressed as mean ± standard deviation. (adapted and newly drawn from Raskovic et al. [109])*

These findings also support a combination of rosemary essential oil with codeine and acetaminophen in the management of pain. The authors came to the conclusion that the essential oil of *R. officinalis* L. shows central analgesic properties and is useful for the management of pain. [109]

De Sousa et al. found out that the naturally occurring monoterpene R-(+)-pulegone significantly inhibits the nociception induced by formalin and hot plate test. Furthermore, the authors suggested that R-(+)-pulegone exerts a central depressant effect due to a *"decrease in ambulation and an increase in pentobarbital-induced sleeping time in mice"*. [110] The same working group also determined the relationship between antinociceptive activity and chemical structure of the monoterpene rotundifolone, which occurs in the essential oil of *Mentha x villosa* Hudson (Lamiaceae), to find out which functional groups are involved. In the acetic acid-induced pain models in mice, all tested monoterpenes showed a greater antinociceptive effect than rotundifolone itself. Morphine was used as positive control substance. They compared rotundifolone with limonene oxide and found out that the absence of the ketone group did not decrease antinociception. Pulegone oxide and carvone epoxide showed greater antinociception thus they suggested that the position of the functional group influences the action. Treatment with (-)-carvone and (+)-carvone had the greatest influence. The results indicate that specific structural modifications affect the analgesic properties. [111]

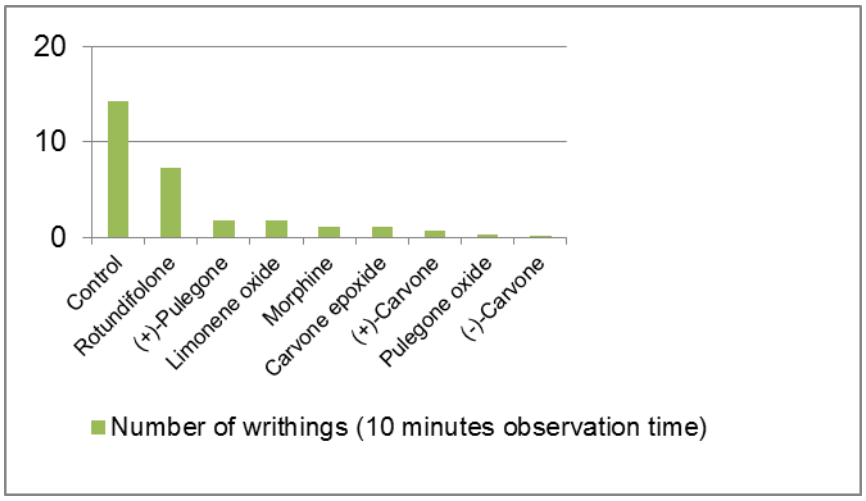


*Figure 3 - Number of writhes after treatment with morphine (3 mg/kg) and compounds (250 mg/kg) after performing the acetic acid-induced writhing test in mice (adapted and newly drawn from de Sousa et al. [111] )*

Peppermint oil also contains pulegone, but the European Pharmacopoeia stipulates a maximum concentration of 4 %. [5] In-vitro studies, performed by Kawata et al., assessed the cyclooxygenase inhibiting effect of monoterpenoids with a p-menthan skeleton. Pulegone, γ-terpinene, α-terpineol and α-carveol acted as a selective cyclooxygenase 2 inhibitor. α-Terpineol showed higher COX-2 inhibition than acetylsalicylic acid. [112]

The aim of the study by da Rocha et al. [113] was to examine the antinociceptive and antiinflammatory properties of α,β-epoxy-carvone in mice. Intraperitoneal administration of the monoterpene at doses of 100, 200 or 300 mg/kg showed a significant antinociception in acid-induced abdominal writhing test. Also the formalin induced nociception decreased in the first (300 mg/kg) and second phase (200 and 300 mg /kg). In the hot plate test they registered an increase of latency time at 30 min (at 100, 200 and 300 mg/kg) and at 60 and 120 min (300 mg/kg) after administration. This effect was reversed by naloxone, so the authors concluded that the pronounced antinociceptive effect of α, β-epoxy-carvone was associated with an activation of the opioidergic system. [113] Oliveira et al. tested whether the synthetic intermediate hydroxydihydrocarvone, which was obtained from R-(-) carvone hydration, has a central antinociceptive effect in intraperitoneal administration. In addition, the authors performed the tail immersion test. Mice which received hydroxydihydrocarvone showed longer response times to the thermal noxious

stimulus. Similar results were achieved, but the effect on the formalin and hot plate tests was not blocked by opioid antagonists. [114] Another popular essential oil is extracted from *Thymus vulgaris* (Lamiaceae). Its main components are thymol and p-cymene. The oil is used as a liniment due to the irritating and stimulating properties. [5] Mikaili et al. revealed that intra-peritoneal injection of 0.1 mg/ml essential oil of *T. vulgaris* led to a significant antinociceptive effect in tail flick test in mice, especially during the first 30 minutes after intervention. After 60 and 90 minutes the observed action wore off. The authors also made the same experiment with the essential oil of *Foeniculum vulgare* (Apiaceae), but there were no significant differences to the control group. Further studies with higher doses of fennel oil are necessary. [115]

Zhang et al. tested the effect of the aroma oils of white pepper (*Piper nigrum* L. (Piperaceae)), long pepper (*Piper longum* L. (Piperaceae)), cinnamon (*Cinnamomum cassia* Presl. (Lauraceae)), saffron (*Crocus sativus* L. (Iridaceae)) and myrrh (*Commiphora myrrha Engl.* (Myrtaceae)) obtained by supercritical fluid $CO_2$ extraction on nociception and inflammation in mice. As described in previous studies, the antinociceptive effect was measured using the acetic acid-induced writhes and hot plate test method. Oral pre-treatment with an essential oil blend significantly reduced the number of writhes triggered by intraperitoneal injection of acetic acid solution in a dose-dependent manner. Treatment with 500 or 1000 mg/kg led to less writhes compared to the reference indometacin. But no significant analgesia on the hot plate pain threshold could be measured. The following major constituents have been analysed by GC/MS: β-selinene, aromadendrene, β-elemene, cis piperitol, cis-β-guaiene, ylangene, 3-heptadecene, δ-cadinene, and β-cadinene. The authors deduced that the essential oil recipe used in their study may be helpful in stroke treatment. [116] The sesquiterpene β-elemene, for example, is able to pass through the blood-brain barrier and may help to resist inflammation caused by stroke. [117]

Jeena et al. [118] dealt with the essential oil isolated from the fruits of *P. nigrum* L. and its pharmacological activities. The authors identified caryophyllene (23.9 %) and limonene (14.4 %) as the main constituents. Black pepper is an old and very popular spice which belongs to the family of Piperacea. Its essential oil is obtained by steam distillation of the fruits. To analyse the antinociceptive activity, 30 mice were divided into five groups. Group 1 acted as the control group, group 2 was treated with acetylsalicylic acid as positive control, group 3, 4 and 5 received 100, 500 and 1000 mg/kg black pepper essential oil intraperitoneally 30 minutes before acetic acid administration. The results revealed a reduced number of writhes (table 4). Aspirin clearly reduced the number of writhes, followed by 500 mg/kg and 1000 mg/kg black pepper oil. The antinociceptive effect of aspirin (73.9 % inhibition) was superior to the essential oil, but especially at doses of 500 and 100 mg/kg, black pepper also showed a significant antinociception compared to the control group. [118]

| Treatment | Number of writhings Mean ± SD | Inhibition (%) |
|---|---|---|
| Control (0.6 % acetic acid) | | 73.0 ± 10.27 |
| 10 mg/kg Aspirin + 0.6 % acetic acid | 19.0 ± 3.87 | 73.97 |
| 100 mg/kg black pepper oil + 0.6 % acetic acid | 62.4 ± 10.99 | 14.52 |
| 500 mg/kg black pepper oil + 0.6 % acetic acid | 38.0 ± 6.63 | 47.94 |
| 1000 mg/kg black pepper oil + 0.6 % acetic acid | 39.2 ± 16.19 | 46.30 |

*Table 4 - This table shows the number of writhes after performing the acetic acid - induced writhing test in mice in the different groups and doses. (newly drawn from Jeena et al. [118])*

Tas et al. compared the essential oil of *Pimpinella anisum* L. with synthetic pain killers using the tail-flick test in mice. The authors found out that anise oil possesses an analgesic potential comparable to morphine and aspirin. [119] Main component of this essential oil, which belongs to the family of Apiaceae, is trans-anethole. [5] Nishijima et al. examined the effect of orally administered citral on chronic and acute pain in rodents. Citral is an essential oil component of several plants, e.g. of *Cymbopogon citratus* (Poaceae) (commonly known as lemongrass). The study showed that *"citral significantly inhibited the neurogenic and inflammatory pain responses"* induced by formalin, glutamate or phorbol-12-myristate-13-acetate injection. It also reduces mechanical

hyperalgesia in a model of postoperative pain in mice. It was found that the antinociceptive action of citral is partly based on activation of 5HT2A serotonin receptor. [120] Melo et al. studied the antinociceptive potential of citronellal, which differs from citral by a missing doublebond, in mice. The number of writhes and paw licks were significantly reduced compared to the control group. Furthermore, the hot plate test showed central analgesic effects. [121]

Another animal model performed by Paula-Freire et al. [122], demonstrated the antinociceptive effect of the orally administrated bicyclic sesquiterpene trans-caryophyllene on acute and chronic pain. It is present in many plants, including *Cannabis sativa* (Cannabaceae), *Ocmium gratissimum* (Lamiaceae) and *Cordia verbenaceae* (Boraginaceae) and acts as an agonist of the cannabinoid CB2-receptor. In the study, acute pain was triggered using the hot plate test for thermal nociception and the formalin test for inflammatory pain. Depending on the dosage, trans-caryophyllene increased the latency to lick or jump from hot plate and attenuates pain in formalin tests compared to the control group. Neuropathic pain induced by chronic sciatic nerve injury was relieved and a decrease in IL-1 β levels was measured. To analyse the mechanism of action, mice were pre-treated with naloxone before trans-caryophyllene treatment. It was established that both, the opioid and endo-cannabinoid system are involved in the observed effects, but further studies are required. It seems that only higher doses of 5 or 10 mg/kg of trans-caryophyllene cause therapeutic effects. [122]

Barocelli et al. [123] described the antinociceptive effect of orally administrated and inhaled essential oil of *L. hybrida* in rodents. The animals received either 100 mg/kg orally, or inhaled 60 minutes. Pain was triggered by acetic acid injection or hot plate. Pre-treatment with the opioid antagonist naloxone, the muscarinic antagonist atropine and the nicotinic antagonist mecamylamin was provided in different sets of mice. Results showed that pretreatment with naloxone prevented the antinociceptive effect in contrast to atropine and mecamylamine in the acetic acid group. In the hot plate test group, the analgesic activity after inhalation was inhibited by naloxone, atropine and mecamylamine pretreatment. The conclusion can be drawn that opioidergic as

well as cholinergic pathways are involved. [123] The monoterpene (-)-linalool is an important constituent of *L. hybrida* essential oil and can also be found in the oils of several other aromatic plants. For example in *Zhumeria majdae* (Lamiaceae) oil in the proportion of 63.4 %. Miraghazadeh et al. examined this particular essential oil and detected a significant decrease in the number of acetic acid - induced writhes compared to placebo in mice. They also noticed central analgesic properties by performing the hot plate test as well as an antiinflammatory potential in carrageenan induced paw edema tests in rats. The effects were similar to those of diclofenac sodium, which acted as standard drug. [124]

Peana et al. performed several studies to characterise the mechanisms which are involved in antinociceptive actions of (-)-linalool: In 2003 the authors analysed the antinociceptive potential of linalool and came to the conclusion that (-)-linalool significantly reduces the acid-induced writhing in mice at doses ranging from 25 to 75 mg/kg. They found out that both, naloxone and atropine reversed this effect, suggesting that cholinergic and opiodergic systems are involved. For the hotplate test, a model for supraspinal analgesia, higher doses of about 100 mg/kg linalool were necessary. A more pronounced effect of (-)-linalool on the writhing test with its antiinflammatory activity was discerned and a possible confounding influence of the sedative effect of this alcohol because of a dose-dependent increase of locomotor activity. [125] One year later a study was published which examined the possible influence of muscarinic M1 receptor antagonist pirenzepine, naloxone, atropine, the dopamine D2 receptor antagonist sulpiride, the dopamine D1 receptor antagonist (R)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine and the ATP-sensitive K+ channel inhibitor glibenclamide on the antinociceptive effect of (-)-linalool in mice. (-)-Linalool at doses of 50 and 100mg/kg led to a significant reduction in the acute early phase, but not in the late phase of the formalin model. Higher doses of 150 mg/kg influenced both phases. 100 and 150 mg/kg also increased the reaction time in the hot plate test. Oral pre-treatment with atropine, naloxone, sulpirid and glibenclamide attenuated the described antinociceptive effects. Pirenzepine and the D2 receptor antagonist did not show these effects. The scientists concluded that the opening of K+ channels

may be a consequence of the M2, opioid and D2 receptor stimulation. These receptors are linked to Gi/G0 proteins. [126] In 2005, the same working group also investigated the effect of this monoterpene alcohol on LPS induced response in a macrophage cell line. The outcome was that the reduction of NO production furnished antinociceptive effects due to an inhibition of nitrite accumulation without inhibiting the LPS-stimulated iNOS expression. However, the *in-vitro* study also showed a failure of this effect if (-)-linalool has not been applied at the highest concentration regarding both the inhibition of PGE2 release and COX2 activity. [127] Further, Peana et al. [128] published that adenosine $A_1$ and $A_{2A}$ receptors are involved in the antinociceptive effect. For testing the effect on mice, the authors used the hot plate test. Besides the important role which adenosine plays as a part of the energy rich molecules ATP and ADP it acts as an endogenous neurotransmitter and modulator via the G protein-coupled family of receptors. [48] It can be concluded that the antinociceptive effects of (-)-linalool occurred at lower doses, at which no side effects regarding the animal's gross behaviour were observed. [128]

Glutamate receptors which are divided into two groups – ionotropic and metabotropic – have a decisive influence in nociceptive processes on spinal and peripheral levels. Ionotropic receptors include: NMDA (N-methyl-D-aspartate), AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) or kainite receptors. [48] In 2008, Batista et al. revealed that (-)-linalool was able to modulate ionotropic glutamate receptors. 20 µl of L-glutamic acid hydrochloride, substance P, kainic acid, tACPD (trans-1,3-dicarboxylic acid), AMPA or NMDA were injected intraplantarly to the right hind paw. The duration rodents licking the injected paw was measured and considered to correspond with nociception. Before this injection, mice were pre-treated with (-)-linalool injection, control animals only received vehicle substance instead. Both systemic and central administration of this monoterpene alcohol led to significant and dose-dependent inhibition of glutamate-induced nociception. Also the biting response induced by glutamate, NMDA, AMPA, substance P and kainate were alleviated. This did not apply for metabotropic glutamatergic receptor agonist trans-ACPD. [129]

Another very interesting animal-study by Ghelardini et al. compared the essential oil of *L. angustifolia* with the two sorts of citrus – *C. reticulata* Blanco and *C. limon* – in localanaesthetic activity. Only the essential oil of lavender was able to reduce drastically the electrically evoked contractions of phrenic-hemidiaphragm in rats as well as to increase the number of stimuli necessary to provoke conjunctival reflexes in rabbits – both in a dose-dependent manner. [130]

A recently published study by Khodabakhsh et al. [131] explored the analgesic and antiinflammatory properties of essential oil of *C. aurantium* L. blossoms, also known as neroli, in mice. Furthermore, they investigated whether nitric oxide / cyclic-guanosine monophosphate pathways are involved in those effects. Neroli oil significantly reduced the number of acetic acid - induced writhes compared to placebo. In the hot plate test, it also increased the latency time significantly. This effect indicates that neroli oil possesses both central and peripheral antinociceptive properties. Diclofenac sodium, which is a NSAID drug with peripheral analgesic effects, acted as positive control. To observe whether the NO/cGMP pathway plays a role in the analgesic activity of neroli oil, mice were pre-treated with L-nitro arginine methyl ester (L-NAME) 0.9 % in a saline solution, a competitive and reversible inhibitor of NO synthase. Neroli oil or sweet almond oil were given 15 minutes after L-NAME as control. Subsequently the hot plate and the acetic acid - induced writhing test were performed. Pre-treatment with L-NAME led to an improvement of the analgesic effect of neroli oil both by producing a change in the number of abdominal constrictions in acetic acid-writhing and hot plate tests. It was also possible to demonstrate the antiinflammatory activity. This effect was similar to those of diclofenac-sodium, especially at doses of 40 mg / kg. Inflammation was triggered by injection of 2 % carrageenan into a hind paw of the rat. The main compounds of the tested oil were linalool (28.5 %), linalyl acetate (19.6 %), nerolidol (9.1 %), *E,E*-farnesol (9.1 %), α-terpineol (4.9 %) and limonene (4.6 %). [131] The US Food and Drug Administration (FDA) approved neroli essential oil as generally regarded as safe (GRAS) for internal consumption. [132]

The involvement of the NO/cGMP pathway also was the focus of a research in animals by Guilhon et al. [133] The authors investigated antiinflammatory and antinociceptive effects of *Lippia gracilis* Schauer (Verbenaceae) essential oil and found out that L-NAME reversed the analgesic activity of the oil. Atropine led to the same effect. In addition, it was figured out that the administration of naloxone exerted no influence on the antinociceptive effect. The methods used to induce the pain were acetic acid - induced contortion, formalin-induced licking and hot plate test. [133] Mendes et al. also carried out a study to examine the essential oil of *L. gracilis Schauer* and its analgesic and antiinflammatory effects. Oral administration at doses of 50, 100 and 200 mg/kg significantly reduced the number of abdominal writhes induced by acetic acid compared to control group. [134] In both studies mentioned above, *L. gracilis* essential oil also showed antiinflammatory activity.

The essential oil from ginger was the focus of a research by Jeena et al. [135] α-Zingiberene (31 %) was identified as the main constituent. 15.4 % ar-curcumene and 14.0 % α-sesquiphellandrene were contained as well. The essential oil showed a significant reduction in acetic acid-induced writhing movements. Additionally, antiinflammatory and antioxidant properties were discovered. [135] Sulaiman et al. [136] also performed chemical and thermal animal models of nociception to evaluate the potential of the volatile oil of *Zingiber zerumbet* (Zingiberceae). Intraperitoneal administration of 30, 100 or 300 mg/kg essential oil led to a significant dose-dependent inhibition of abdominal writhings, comparable to acetylsalicylic acid. It also had a positive effect on the latency time during the hot plate test as well as the formalin-induced paw licking test. The main compounds were zerumbone and camphene. Furthermore, an involvement of the opioid system in the analgesic effect of the essential oil by administration of naloxone was noticed. [136]

Khalid et al. also tested the essential oil of *Z. zerumbet* and found out that its antinociceptive properties are probably based on an inhibition of the glutamatergic system and TRPV1 receptors, as well as an activation of the *"L-arginine/nitric oxide/cGMP/protein kinase C/ATP-sensitive K+ channel pathway".* [137]

De Araùjo et al. [138] observed the effect of orally administered *Alpinia zerumbet* (Pers.) Burtt. et Smith essential oil in mice. In the acetic acid-induced writhing test, the oil was effective at doses of 30, 100 and 300 mg/kg. In the hot plate test, the latency time was increased only at doses of 100 and 300 mg/kg. In the formalin test, the paw licking time was reduced at 100 mg/kg in the second phase, but inconsistently the time was longer at 300 mg/kg at both phases. At 30 mg/kg no difference compared to the control group could be detected. The results suggested that the explored essential oil possesses a dose-dependent antinociceptive effect. It was also found that opioid receptors may be involved. [138]

In folk medicine, the essential oil of *Laurus nobilis* is externally used in treatment of rheumatic pain and hyperaemia. Key ingredients of the leaf essential oil of *L. nobilis* include 1,8-cineole, α-and β-pinene , citral and terpineol.[65] α-pinene, β-pinene and sabinene have already been known for their antiinflammatory activity. This knowledge is based on experimental models. [139] [140] A study by Sayyah et al. explored the possible analgesic and antiinflammatory effect of the leaf essential oil of *L. nobilis* in tail-flick and formalin tests in mice and rats compared to piroxicam and morphine. The essential oil inhibited the progressive increase in paw edema triggered by formalin, similarly to piroxicam in a dose-dependent manner. The antiinflammatory effect of this essential oil occurred later compared to synthetic piroxicam. Antinociception triggered by the essential oil at the dose of 0.06 ml/kg was similar in potency and early onset of action like morphine and not reversible by naloxone; hence it was concluded that the endogenous opioid system is not involved in the analgesic activity of this essential oil. A high dose of the essential oil led to a strong sedation. Further investigation is necessary to definitely identify active compounds as well as the exact mechanism of action. [141]

Hart et al. found out that tea tree oil of *Melaleuca alternifolia*, which contains 4-terpineol as main-component, suppresses the production of inflammatory mediators by activated human monocytes. [142] In the study of Rabelo et al., the essential oil of *Remirea maritima Aubl.* (Cyperaceae) from roots and

rhizomes showed central and peripheral analgesic effects after oral administration. The authors used the acetic acid writhing reflex, formalin-induced nociception and carrageenan-induced edema test in mice.
Identified compounds were 43.2 % remirol, 13.8 % cyperene, 5.8 % iso-evodionol, 5.7 % cyperotundone, 4.9 % caryophyllene oxide and 4,6 % rotundene. [143]

A recent study published in 2015 by Khalilzadeh et al. investigated the antinociceptive activity of *Vitex agnus-castus* (Verbenaceae) essential oil. α–pinene (14.8 %), limonene (10.3 %), β–caryophyllene (6.9 %), sabinene (5.3 %), and β–farnesene (5.9 %) were identified as the major components. The essential exerted a pain reduction in both tail immersion and formalin test in male rats. This effect was reversed by naloxone and atropine which suggests that both opioidergic and cholinergic systems were involved. In acetic acid-induced writhing response test the essential oil also showed analgesic effects. [144]

# 4 Overview

## Palliative Care and Hospices

### MOUTH CARE

- *Cranesbill (Geranium sp.)*
- *Lavender (Lavandula sp.)*
- *Tea tree (Melaleuca alternifolia)*
- *Manuka (Leptospermum scoparium)*
- *Kanuka (Kunzea ericoides)*
- *Peppermint (Mentha x. piperita)*
- *Lemon (Citrus limon)*

### WOUND MANAGEMENT

- *Tea tree (Melaleuca alternifolia)*
- *Eucalyptus sp.*
- *Lemongrass (Cymbopogon sp.)*
- *Lemon (Citrus sp.)*
- *Clove (*Syzygium aromaticum)

### CANCER

- *Roman chamomile (Chamaemelum sp.)*
- *Bitter orange (Citrus x. aurantium)*
- *Lavender (Lavandula angustifolia)*
- *Sandalwood (Santalum album)*
- *Bergamot (Citrus sp.)*
- *Frankincense (Boswellia sp.)*
- *Rosewood (Aniba sp.)*
- *Rose (Rosa sp.)*
- *Valerian (Valeriana sp.)*

### NAUSEA

- *Fennel (Foeniculum vulgare var dulce)*
- *Anise (Pimpinella anisum)*
- *Chamomile (Anthemis nobilis)*
- *Peppermint (Mentha x piperita)*
- *Spearmint (Mentha spicata)*
- *Ginger (Zingiber sp.)*
- *Cardamom (Elettaria sp.)*

### GASTROINTESTINAL SYMPTOMS

- *Bitter orange (Citrus sp.)*
- *Black pepper (Piper sp.)*
- *Rosemary (Rosmarinus sp.)*
- *Marjoram (Origanum majorana)*
- *Geranium (Pelargonium sp.)*
- *German chamomile (Matricaria recutita)*
- *Patchouli (Pogostemon cablin)*

## Animal Studies

| ANIMAL STUDIES |
| --- |
| • *Cannabis (Cannabis sativa)*<br>• *Basil (Ocmium gratissimum)*<br>• *Cordia (Cordia verbenaceae)*<br>• *Lavender (Lavandula hybrida, L. angustifolia)*<br>• *Zhumeria (Zhumeria majdae)*<br>• *Lippia gracilis Schauer*<br>• *Ginger (Zingiber zerumbet)*<br>• *Shell ginger (Alpinia zerumbet)*<br>• *Laurel (Laurus nobilis)*<br>• *Tea tree (Melaleuca alternifolia)*<br>• *Remirea maritima*<br>• *Monk's pepper (Vitex agnus-castus)*<br>• *Laserpitum ochridanum*<br>• *Laserpitum zernyi*<br>• *Rainforest plum (Eugenia candolleana DC.)*<br>• *Melissa (Melissa officinalis)*<br>• *Tarragon (Artemisia dranunculus)*<br>• *River Red Gum (Eucalyptus camaldulensis)*<br>• *Croton cordiifolius Baill.*<br>• *Rosemary (Rosmarinus officinalis)*<br>• *Mojito mint (Mentha x villosa Hudson)*<br>• *Thyme (Thymus vulgaris)*<br>• *White pepper (Piper nigrum)*<br>• *Long pepper (Piper longum)*<br>• *Cinnamomum cassia Presl*<br>• *Saffron (Crocus sativus L.)*<br>• *Myrrh (Commiphora myrrha Engl.)*<br>• *Anise (Pimpinella anisum L.)*<br>• *Lemongrass (Cymbopogon citratus)* |

## Pain-therapy

### GYNAECOLOGY

- Lavender (Lavandula officinalis and Lavandula angustifolia)
- Clary sage (Salvia sclarea)
- Salvia (Salvia officinalis)
- Marjoram (Origanium majorana)
- Rose (Rosa centifolia, Rosa sp.)
- Cinnamon (Cinnamomum cassia)
- Clove (Syzygium aromaticum)
- Peppermint (Mentha x. piperita)
- Bitter orange (Citrus x. aurantium)
- Mandarin orange (Citrus reticulata)
- Jasmine (Jasminum sp.)
- Chamomile (Chamaemelum nobile)
- Frankincense (Boswellia carteri)

### RHEUMATIC AND NEURALGIC DISCOMFORT, MUSCLE STRAINS (COUNTER IRRITANTS)

- *Clove (Syzygium aromaticum)*
- *Cinnamon leaf (Cinnamomum cassia)*
- *Eucalyptus (Eucalyptus sp.)*
- *Wintergreen (Gaultheria procumbens)*
- *Camphor (Cinnamomum camphora)*
- *Laurel (Laurus nobilis)*
- *Juniper (Juniperus communis)*
- *Lavender (Lavandula sp.)*
- *Pine (Pinus sp.)*
- *Spruce (Picea sp.)*

### NECK PAIN

- *Marjoram (Origanum majorana)*
- *Black pepper (Piper nigrum)*
- *Lavender (Lavandula sp.)*
- *Peppermint (Mentha x. piperita)*

### SHOULDER PAIN

- *Lavender (Lavandula sp.)*
- *Rosemary (Rosmarinus sp.)*
- *Peppermint (Mentha x. piperita)*

### HEADACHE

- *Peppermint (Mentha x piperita)*
- *Lavender (Lavandula sp.)*

### KNEE PAIN

- *Ginger (Zingiber officinale)*
- *Orange (Citrus sinensis)*

**LOCAL ANAESTHESIA**

- *Clove (Syzygium aromaticum)*
- *Myrrh (Commiphora molmol)*

**POSTOPERATIVE PAIN**

- *Lavender (Lavandula angustifolia and L. officinalis)*
- *Rose (Rosa damascene Mill.)*

**BACK PAIN**

- *Ginger (Zingiber sp.)*

**CARPAL TUNNEL SYNDROME**

- *Menthol (Mentha sp.)*

**HAEMODIALYSIS**

- *Lavender (Lavandula sp.)*

**MUSCLE STRAIN**

- *Methyl salicylate (Gaultheria procumbens and Betula lenta)*

**TOOTHACHE**

- *Clove (Syzygium aromaticum)*

# 5 Concluding remarks

There are many studies about essential oils in palliative care which are mostly about complementary and alternative treatment methods. Massage has often been performed but without stating the used essential oils and their compounds. In order to be able to make a scientifically objective statement, further studies are necessary to get more accurate information.

Cancer patients often have to take a combination of many drugs simultaneously which causes a lot of unpleasant side effects. Aromatherapy can be useful to relieve these patients from nausea, increase their sense of well-being and help them to relax.

Literature also refers to a number of studies dealing with essential oils against pain. For example women during pregnancy and child birth are benefiting from the analgesic properties and low side effects because the therapeutic options are limited. Considering that patients suffering from headaches are frequently struggling with medication induced headache, which is a consequence of the overuse of medication, essential oils, especially peppermint oil, represent a great alternative to them.

As many studies used animal experiments the results probably cannot be applied to human. Furthermore, one has to argue that animal tests are ethically contentious. However, animal experiments are well suited to assess exact mechanisms of action including the involved receptors. It could be shown that the opioidergic, glutamatergic, serotoninergic and cholinergic systems are involved frequently. Further studies should particularly focus on the application in humans. But the already executed trials and studies however, showed a significant potential for the application of essential oils against pain.

To sum up, essential oils and their compounds are well suited for the application in palliative care, hospices and against pain. They provide a good treatment option, both complementary to conventional methods and as sole therapy against mild complaints. Furthermore, the use of essential oils is accompanied with few side effects and well-tolerated by patients.

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# 7 List of figures

Figure 1 - The visual analogue scale (VAS) is often used to rate the intensity of felt pain. (newly drawn from Hospice Education Institute [57])

Figure 2 - The figure demonstrate the satisfaction (%) with the therapy and the frequency (%) of patients need to take additional diclofenac suppository for analgesia. (newly drawn according to Olapour et al. [81])

Figure 3 - Number of writhes after treatment with morphine (3 mg/kg) and compounds (250 mg/kg) after performing the acetic acid-induced writhing test in mice (adapted and newly drawn from de Sousa et al. [111] )

# 8 List of tables

Table 1 - This table shows the average pain scores and standard deviations of primiparae in the different cervical dilations according to study groups. (Newly drawn according to Namazi et al. [80] )

Table 2 - The table shows the mean VAS and standard deviations before, 30 and 60 minutes after the treatment in primiparous women with cervical dilation of 3-4 cm. (newly drawn according to Kaviani et al. [84])

Table 3 - The table shows the response latency time to heat-induced pain in the different groups in seconds. All values are expressed as mean ± standard deviation. (adapted and newly drawn from Raskovic et al. [109])

Table 4 - This table shows the number of writhes after performing the acetic acid - induced writhing test in mice in the different groups and doses. (newly drawn from Jeena et al. [118])

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