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AROMATHERAPY AS AN ADJUVANT TREATMENT IN CANCER CARE – A DESCRIPTIVE SYSTEMATIC REVIEW

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Abstract

Claims of benefits of aromatherapy for cancer patients include reduced anxiety levels and relief of emotional stress, pain, muscular tension and fatigue. The objective of this paper is to provide an updated descriptive, systematic review of evidence from pre-clinical and clinical trials assessing the benefits and safety of aromatherapy for cancer patients. Literature databases such as Medline (via Ovid), the Cochrane database of systematic reviews, Cochrane Central were searched from their inception until October 2010. Only studies on cancer cells or cancer patients were included. There is no long lasting effect of aromatherapy massage, while short term improvements were reported for general well being, anxiety and depression up to 8 weeks after treatment. The reviewed studies indicate short-term effects of aromatherapy on depression, anxiety and overall wellbeing. Specifically, some clinical trials found an increase in patient-identified symptom relief, psychological wellbeing and improved sleep. Furthermore, some found a short-term improvement (up to 2 weeks after treatment) in anxiety and depression scores and better pain control. Although essential oils have generally shown minimal adverse effects, potential risks include ingesting large amounts (intentional misuse); local skin irritation, especially with prolonged skin contact; allergic contact dermatitis; and phototoxicity from reaction to sunlight (some oils). Repeated topical administration of lavender and tea tree oil was associated with reversible prepubertal gynecomastia.

Key words: aromatherapy, essential oil, massage, cancer, review

Introduction

Aromatherapy encompasses the use of essential oils derived from different types of plant sources for a variety of application methods. Generally, the whole fresh plant (not crushed or powdered) is used for the essential oil distillation process. The specific ingredients of an essential oil are derived from plant materials or parts that are claimed to possess therapeutic properties. Essential oils are “the steam distillate of aromatic plants” (Tisserand and Balacs, 1995). They have been described as “the volatile, organic constituents of fragrant plant matter and contribute to both flavor and fragrance and are extracted either by distillation or by cold pressing (expression)" (Tisserand and Balacs, 1995). The history of distillation of essential oils started with the medieval physician Avicenna (Abu Ali al-Hussein Ibn Abdallah Ibn Sina; 980 - 1037) from Persia who invented the process of distillation and was probably the first to distil oil of the rose plant (Tisserand, 1988). Today, approximately 40 different oils derived from plants are used in aromatherapy. Lavender, rosemary, eucalyptus, chamomile, marjoram, jasmine, peppermint, lemon, ylang ylang, and geranium are some of the most popular.

The term ‘aromatherapy’ was coined by French chemist and perfumiér René Maurice Gattefossé in the 1920s and is a subcategory of ‘herbal medicine’ (Gattefosse, 1993). Gattefossé's book was published in 1937. He suggested that aromatherapy could be used to treat diseases in virtually every organ system, citing mostly anecdotal and case-based evidence. In the 1960s, aromatherapy was revived by the French homeopath Dr. Maury, and in the 1980s it increased in popularity in the United States. It is fairly well-established in Australia, Canada, France, Germany, New Zealand, Switzerland and the UK.

There are various forms of application. Most commonly, oils are applied topically in diluted forms, often together with a carrier oil as part of massage therapy to manipulate the soft tissue of the body, or by using an incense burner for inhalation of the aroma. Essential oils may be inhaled by adding a few drops to steaming water, thereafter an atomizer or humidifier spreads the aroma throughout the room. Certain aromatherapy oils are also ingested through teas, whereas others can be added to bathwater or pillows, or used to make ointments, creams and compresses. Some aromatherapists argue that the use of certain herbs in food can also be considered part of aromatherapy, although this should be considered as a specific alimentation rather than a precise use as essential oils.

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Essential oils are supposed to improve physical and emotional wellbeing (www.cancer.gov/cancertopics/-pdq/cam/aromatherapy/healthprofessional.page1). A wide range of claims for the effect of certain oils have been put forward, ranging from: to affect a patient's "subtle body"; bring balance to a distinct "chakra"; restore harmony to the "energy flow"; become centered; contribute to "spiritual growth"; alter mood and improve overall health; to more specific claims such as having anticonvulsive and spasmolytic properties (www.skepdic.com/aroma.html). It has been suggested that the topical application of aromatic oils may exert antibacterial, anti-inflammatory, and analgesic effects.

For cancer patients, claims of benefits include reduced anxiety levels and relief of emotional stress, pain, muscular tension and fatigue (Fellowes et al, 2004). Some of these alleged outcomes are vaguely defined.

The chemical properties and composition of a specific type of oil gives it whatever therapeutic qualities the essential oil might have. A number of theories try to explain the mechanism of action of aromatherapy and essential oils. The most often cited is the proposed connection between olfaction and the limbic system in the brain as the basis for the effects of aromatherapy on mood and emotions (Smith, 1999). These assertions have been contested by the biochemistry and psychology communities, which take a different view of the possible mechanism of action of odors on the human brain and do not differentiate the odors produced by essential oils from those of synthetic fragrances (Perry and Perry, 2006). Little is said about proposed mechanisms for its effects on other parts of the body. Unfortunately, many of these assumptions are primarily theoretical because of the lack of significant research addressing this topic. There is also a lack of in-depth neurophysiological studies on the nature of olfaction and its link to the limbic system.

An individual's expectation and subjective perception of oil supposedly influences treatment outcomes, including whether or not an individual has previous experience with a particular scent and whether it is perceived as pleasurable (www.sirc.org/publik/small.pdf). Marked association of odors with emotional response has been shown to be due to the prominence of afferent links from the olfactory bulb to the amygdala, where emotional significance is attached to incoming stimuli (Clark and Boutros, 1999).

Neuro-chemical aspects involve a suggested inhibition of glutamate binding, γ-amiobutyric acid (GABA) augmentation and acetylcholine receptor binding. As an example, the main terpenoid component of lavender oil is linalool. Linalool has been shown to inhibit glutamate binding in rats (Watt, 1995) and inhaled lavender oil reduces electroshock-induced convulsions in mice, which suggests augmentation of GABA (Yamada et al, 1994). Linalool's inhibitory effect was demonstrated to be dose dependent with increasing concentrations; all response was abolished by the use of 6.5 mM linalool. This modifying effect on the glutamatergic system is comparable with phenobarbital, a known anticonvulsant (Elisabetsky et al, 1995). Further evidence for this mechanism comes from the finding of a potentiation of GABA receptors expressed in Xenopus oocytes by lavender oil components (Aoshima et al, 2001).

It has been suggested that compounds from essential oils may enter the body (via the olfactory mucosa or the bloodstream by lung absorption) and may directly influence the brain (Watt, 1995). It is suggested that there are scent receptors in the nose which send chemical messages via the olfactory nerve to the brain's limbic region. This in return can affect a person's emotional responses, heart rate, blood pressure and breathing.

Generally speaking, the application of aromatherapy is suggested to help patients cope with stress, chronic pain, nausea and depression. One can assume both direct effects of the oils, but also positive expectations of the patients. Furthermore it has been suggested that the use of essential oils can relieve bacterial infections (Geda, 1995), stimulate the immune system (Komori et al, 1995), help to fight colds, flues and sore throats (Hasani et al, 2003), improve urine production (Morimoto and Shibata, 2010), increase circulation (Shiina et al, 2008) and aid in the healing of cystitis (Eriksen, 2000), herpes simplex (Buckle, 2002), acne (Eriksen, 2000), headaches (Eriksen, 2000), indigestion (Schnaubelt, 1999), premenstrual syndrome (Eriksen, 2000), muscle tension (Lis-Balchin et al, 2000), and even cancer (Fellowes et al, 2004). Specific indications can only be discussed by choosing a selected number of essential oils.

In Australia, three surveys showed that up to 1% of cancer patients used aromatherapy (Girgis et al, 2005, Salminen et al, 2004, Correa-Velez et al, 2003). In Canada, two surveys revealed that up to 4% of cancer patients used it (Tough et al, 2002, McKay et al 2005). In Italy, Spain and Turkey prevalence ranges from <1 to 2% (Johannessen et al, 2008, Fernandez-Ortega et al, 2008, Akyuz et al, 2007). In contrast, six surveys carried out in the UK showed that 40.6% of cancer patients were using it (Lewith et al., 2002, Maher et al., 1994, Rees et al., 2000, Harris et al., 2003, Scott et al., 2005, Shakeel et al., 2008). A US survey revealed that 11% of cancer patients may be using aromatherapy and in New Zealand 6% (Lawsin et al., 2007, Chrystal et al., 2003). However, it is unclear whether this usage is a specific anti-cancer intervention or simply to increase general well-being and thus life-style associated rather than a therapeutic approach. One could assume that a similar percentage of healthy individuals is using essential oil, too.

Since aromatherapy can also be applied orally or rectally, the administration of such oils may not be legally permitted in several countries, unless it is applied by a medically qualified person. There may be legal issues resulting from the fact that diluted essential oils can "penetrate the skin", which could be considered as administering a drug. This review was carried out as a project for the European CAM cancer consortium (www.cam-cancer.org) and includes studies which assess the effect of aromatherapy on its own or in conjunction with massage therapy. The objective of this paper is to provide an updated review of evidence from pre-clinical and clinical trials assessing the benefits and safety of aromatherapy for cancer patients.

Methods

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Literature databases such as Medline (via Ovid), the Cochrane database of systematic reviews, Cochrane Central were searched from their inception until October 2010. The main search terms were 'aromatherapy' AND 'cancer'. For specific literature search procedures see Table 1 (OVID) and Table 2 (Cochrane Central and Cochrane database of systematic reviews).
As this review was supposed to be comprehensive, we decided to also include results from pre-clinical studies on cancer cells. Thus, studies on cancer cells or cancer patients were included. The quality of publications was assessed by looking at the internal validity (study design and conduct), external validity (applicability and generalizability of results) and summarizing the direction of evidence (positive, uncertain, negative).

Results

One systematic review, 18 clinical trials and a selected number of pre-clinical trials are summarized here. Further data are presented in Tables 3 and 4. Safety aspects are also discussed.

Systematic reviews

Yim et al (2009) carried out a systematic review specifically including trials for aromatherapy for depression (Yim et al., 2009). They included six studies applying aromatherapy massage in patients with depression. Three of the included studies evaluated the benefit of Swedish massage (two with lavender oil) for depressive symptoms of patients with cancer (mainly women with breast cancer). Results showed significant short term-improvement in anxiety and/or depression compared with usual care. No effect sizes were described. According to the authors this might be explained by an induction of a relaxation response in the autonomic nervous system. However, there was no adequate control intervention (i.e., massage without essential oils), and thus the relevance of this finding remains elusive.

Clinical trials

All clinical studies which applied essential oils with or without massage to cancer patients were included. For the data selection process see flow diagram. A total of 18 clinical studies have been included in this review (Barclay et al., 2006; Chang 2008; Corner et al., 1995; Evans, 1995; Graham et al., 2003; Gravett, 2001a,b; Hadfield, 2001; Imanishi et al., 2009; Kirshbaum 1996, Kite et al., 1998, Louis & Kowalski 2002, Maddocks-Jennings et al., 2009, Soden et al., 2004, Stringer et al., 2008, Wilcock et al., 2004; Wilkinson et al., 1999; Wilkinson et al., 2007). Nine are randomised controlled studies (Barclay et al., 2006; Chang 2008; Corner et al., 1995; Maddocks-Jennings et al., 2009; Soden et al., 2004; Stringer et al., 2008; Wilcock et al., 2004; Wilkinson et al., 1999; Wilkinson et al., 2007), two are controlled (Graham et al., 2003; Louis and Kowalski 2002), three are uncontrolled (Gravett, 2001a,b; Hadfield, 2001) and four are case series (Evans, 1995; Imanishi et al., 2009; Kirshbaum, 1996; Kite et al., 1998) (see Table 3). The evidence of these trials points to a short-term benefit of aromatherapy / essential oils which could possibly last up to 2 weeks with reduction in anxiety and depression scores, improved sleep and an overall increase in wellbeing. Some of these trials also found an increase in patient-identified symptom relief and psychological wellbeing. However, other trials did not report any significant difference between groups. Since the comparator interventions used in the included trials vary greatly, it is not possible to assess the system and component efficacy of specific essential oils. The quality of publications ranged from mediocre to low. Double-blinding is practically impossible in the field of aromatherapy.

In conclusion, existing evidence provides weak evidence that aromatherapy might have some short-term effects on anxiety and depression, and possibly on pain relief. However, it is unclear whether this is a matter of positive expectation or a pharmacologically mediated effect.

Pre-clinical trials

There is considerable published research available on the *in vivo* and *in vitro* anti-inflammatory, anti-oxidant, antibacterial, antifungal, and antiviral activity of a number of essential oils. Furthermore, the cytotoxic, free radical scavenging, carcinogenetic, apoptosis inducing and anti-neoplastic effects of a number of essential oils has been investigated in pre-clinical trials (Gould, 1997). For a summary of the selected pre-clinical studies see Table 4 (Abe et al., 2003; de Sousa et al., 2004; Legault et al., 2007; Ait Mbarek et al., 2007a, b; Horvathova et al., 2007; Atsumi et al., 2007; Banerjee et al., 1994; Li et al., 2004; Xiao et al., 2008; Paik et al., 2005; Crowell et al., 1992). However, the concentrations applied in the respective studies might not be comparable to those in conventional aromatherapy, either volatile or directly resorbed.

Safety aspects

It is generally accepted by aromatherapists that a safe and effective dilution for most aromatherapy/essential oils in

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Table 1: OVID search strategy and results
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present

ID	Search	Hits
1	exp Neoplasms/	2130453
2	exp Lymphoma/	127705
3	exp Leukemia/	174262
4	exp Carcinoma/	404411
5	(cancer* or carcino* or tumor* or tumour* or neoplasm*).ti,ab.	1625323
6	(leukaemi* or leukemi*).ti,ab.	176119
7	malign*.ti,ab.	324193
8	lymphoma*.ti,ab.	105030
9	Antineoplastic.ti,ab.	10777
10	(melanoma* or sarcoma* or adenosarcoma* or adenocarcinoma* or carcinosarcoma* or chrondosarcoma* or fibrosarcoma* or dermatofibrosarcoma* or neurofibrosarcoma* or hemangiosarcoma* or leimyosarcoma* or liposarcoma* or lymphangiosarcoma* or myosarcoma* or rhabdomyosarcoma* or myxosarcoma* or osteosarcoma*).ti,ab.	223542
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	2541534
12	exp Aromatherapy/	413
13	aromatherapy.ti,ab.	424
14	aroma therapy.ti,ab.	22
15	(essential adj oil*).ti,ab.	4468
16	12 or 13 or 14 or 15	4937
17	11 and 16	236
18	Controlled clinical trial.pt.	81735
19	Randomized controlled trials/	67475
20	Random allocation/	68683
21	Double-blind method/	106970
22	Single-blind method/	14058
23	Clinical trial.pt.	462751
24	exp Clinical Trial/	614064
25	(clinic* adj25 trial*).ti,ab.	182717
26	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind*)).ti,ab.	106315
27	Placebos/	28936
28	Placebo*.ti,ab.	126927
29	Random.ti,ab.	126298
30	Research design/	59472
31	Comparative study/	1486610
32	exp evaluation studies/	135441
33	Follow-up studies/	405615
34	Prospective studies/	281016
35	(control* or prospective* or volunteer*).ti,ab.	2297164
36	Cross-over studies/	26085
37	systematic review.ti,ab.	19995
38	meta-analysis.ti,ab.	24945
39	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	4331158

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40	17 and 39	81

Table 2: Cochrane Central and Cochrane database of systematic reviews

ID	Search	Hits
#1	MeSH descriptor Neoplasms explode all trees	40125
#2	MeSH descriptor Lymphoma explode all trees	1878
#3	MeSH descriptor Leukemia explode all trees	2738
#4	MeSH descriptor Carcinoma explode all trees	6882
#5	(cancer* or carcino* or tumor* or tumour* or neoplasm*):ti,ab	54094
#6	(leukaemi* or leukemi*):ti,ab	5225
#7	malign*:ti,ab	5697
#8	lymphoma*:ti,ab	3255
#9	Antineoplastic:ti,ab	290
#10	(melanoma* or sarcoma* or adenosarcoma* or adenocarcinoma* or carcinosarcoma* or chrondosarcoma* or fibrosarcoma* or dermatofibrosarcoma* or neurofibrosarcoma* or hemangiosarcoma* or leimyosarcoma* or liposarcoma* or lymphangiosarcoma* or myosarcoma* or rhabdomyosarcoma* or myxosarcoma* or osteosarcoma*):ti,ab	3610
#11	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)	72033
#12	MeSH descriptor Aromatherapy explode all trees	78
#13	aromatherapy:ti,ab	94
#14	aroma therapy:ti,ab	10
#15	(essential NEXT oil*):ti,ab	172
#16	(#12 OR #13 OR #14 OR #15)	262
#17	(#11 AND #16)	21

massage therapy is a maximum of 2.5 % for adults, which translates to 2 drops of essential oil per 100 drops of carrier oil (2% dilution: 10-12 drops of essential oil per ounce of carrier oil). For full-body baths, the dosage of essential oil is usually 5–10 drops per bath. As long as practitioners know how to dilute them, non-toxic essential oils used on the skin are unlikely to harm the patient.

The testing of essential oils for safety has shown minimal adverse effects. A number of oils have therefore been approved for use as food additives and are classified as GRAS (generally recognized as safe) by the U.S. Food and Drug Administration (US Food and Drug Administration). There is, however, a risk involved with ingestion of large amounts of essential oils. For instance, severe, extensive, life threatening phototoxic reactions, such as the case of a woman who died of a massive phototoxic skin reaction, have been described after ingestion of food and medication containing psoralen and subsequent exposure to artificial UV radiation (Kaddu et al., 1998).

Some essential oils (e.g. camphor oil) can cause local irritation. The main safety issue with essential oils seems to be that cases of contact dermatitis have been reported, mostly in aromatherapists who have had prolonged skin contact with oils in the context of aromatherapy massage. In a mailed 2004 survey including members of a national massage therapy organization in the greater Philadelphia region found that the 12-month prevalence of hand dermatitis in subjects was 15% by self-reported criteria and 23% by a symptom-based method (Crawford et al., 2004). This problem had also been reported much earlier in the UK (Bilsland and Strong, 1990).

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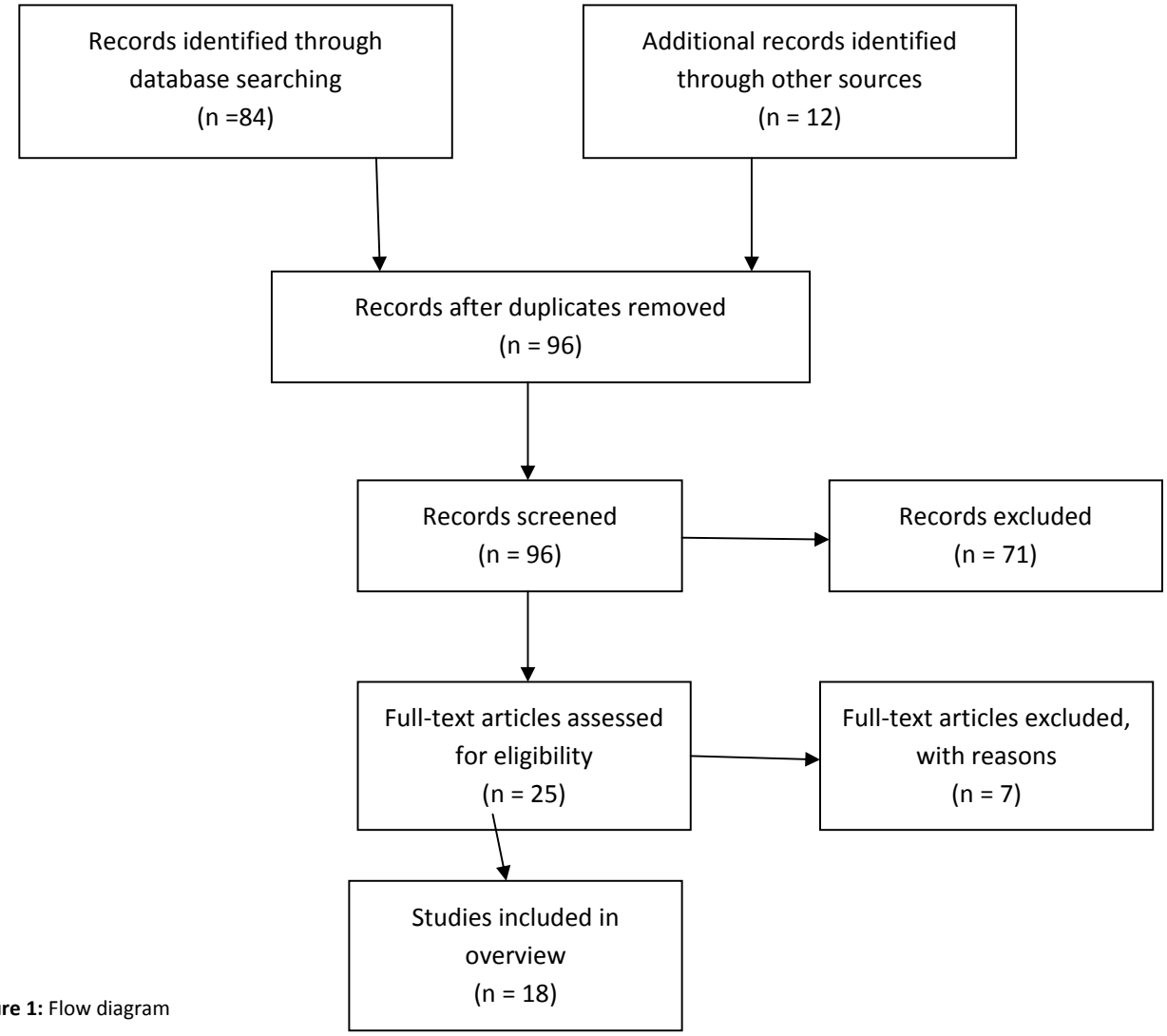

Figure 1: Flow diagram

It has been suggested that since fragrance ingredients are still major causes of allergic contact dermatitis, the concentration of essential oils and materials with unknown composition can be problematic (Jansson and Loden 2001). Moreover, phototoxicity may occur when essential oils (particularly citrus oils) are applied directly to the skin before sun exposure (Kaddu 2001). Individual psychological associations with odors may result in adverse responses, especially if the memory of a scent provokes strong emotions (Holmes and Ballard 2004).

Repeated exposure to lavender and tea tree oils by topical administration was shown in one study to be associated with reversible prepubertal gynecomastia (Henley et al., 2007). The respective effect appears to have been caused by the purported weak estrogenic and antiandrogenic activities of lavender and tea tree oils. Therefore, these two essential oils could cause problems in patients with estrogen-dependant tumors. A review on the safety assessment of St John's Wort (*Hypericum perforatum)* oil concluded that the available data are insufficient to support the safety of ingredients from this plant in cosmetic formulations (Anonymous, 2001).

Discussion

Findings on the interventional use of aromatherapy in cancer patients suggests a short-term benefit to reduce anxiety and depression, improve sleep and increase overall wellbeing; this effect has been suggested to last up to 2 weeks. Some of the trials

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Table 3: Results – extracted data of included studies

First author, year	Type of study	Participants (diagnosis, N)	Arms	Intervention groups, Duration of application, Time of follow-up	Results (sig.)	Comments
Barclay, 2006	RCT	Lymphedema, 81	2	(1) Aromatherapy and massage (2) Massage therapy alone Daily self-massage of limb(s) 6 months	Increase in patient-identified symptom relief (MYMOP) after 6 months (p<0,001) and wellbeing (P=0.003)	Essential oils did not influence improvements in selected outcome measures
Chang, 2008	RCT	Terminally ill patients with various cancer types, 58	2	(1) Aromatherapy hand massage (Bergamot, Lavender, Frankincense) (2) General oil hand massage 5 mins for 7 days 1 week	(1) showed more significant changes in pain (P=0.001) and depression scores (P=0.000)	Aromatherapy hand massage had positive effect on pain and depression
Corner, 1995	RCT	Various types of cancer, 51	2	(1) Massage with an essential oil mix (2) Massage with carrier oil 30 min sessions weekly for 8 weeks 2 months	Anxiety scores (HADS) were significantly reduced over time in the massage with essential oils group only (p<0.05)	Patients in both groups improved over time according to the symptom distress scale
Evans, 1995	Case series	Various types of cancer, 69	Na	Application of various oils and massage therapy Not reported Not reported	General improvement in symptoms reported	No p-values provided
Graham, 2003	CCT	Various types of cancer, 313	3	(1) Aromatherapy including carrier oil with fractionated oils (2) carrier oil only (3) pure essential oils (lavender, bergamot, cedar wood) 15-20 min exposure to oils on bib One-off treatment during radiotherapy	Group (2) had significantly reduced anxiety scores after treatment as measured with HADS (P=.04)	Aromatherapy as administered in this particular trial was not beneficial to cancer patients
Gravett, 2001	UCT	?	Na	Effect of essential oils such as lavender, eucalyptus (Eucalyptus globulus Labill. and Eucalyptus radiata Sieber ex DC. [Myrtaceae]), and tea tree oil was measured on incidence of infections Not reported Not reported	No effects were observed	No patient-generated data from validated outcome measures and no baseline assessment
Gravett, 2001	UCT	?	Na	Orally applied geranium (Pelargonium species), German chamomile (Matricaria recutita L. [synonyms: Matricaria chamomilla L., Chamomilla recutita (L.) Rausch.]), patchouli (Pogostemon cablin [Blanco] Benth. [Lamiaceae]	No effect of essential oils on cancer-related symptoms. Also, no effects on gastrointestinal symptoms	No patient-generated data from validated outcome measures and no baseline assessment

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				[synonyms: Mentha cablin Blanco, Pogostemon patchouly Letettier]), and turmericphytol Not reported Not reported		
Hadfield, 2001	UCT	Malignant brain tumor, 8	Na	Aromatherapy massage (lavender or Roman chamomile) and Enya music 30 min, one-off treatment 24 hours	Decrease in systolic and diastolic blood pressure, heart and respiratory rate	Semi-structured interviews carried out one week after treatment revealed that patients felt more 'relaxed' and 'less tense'
Imanishi, 2009	Case series	Mamma carcinoma, 12	Na	30 min aromatherapy massage twice a week for 4 weeks 1 month	STAI was reduced after a 30 min aromatherapy massage and also reduced in 8 sequential aromatherapy massage sessions in the HADS (P=0.01).	Aromatherapy massage may ameliorated the immunologic state
Kirshbaum, 1996	Case series	Mamma carcinoma with lymphedema, 8	Na	20-30 minute aromatherapy massage with lavender oil Up to 6 sessions Length of follow-up not reported	Reported alleviation of pain, noticeable reduction in swelling, increase in overall comfort and a feeling of relaxation	No p-values provided
Kite, 1998	Case series	Various types of cancer, 89	Na	6 sessions of aromatherapy massage Not reported Not reported	Improvement in HADS scores ($P < 0.001$) as well as symptoms from before baseline to after treatment	-
Louis, 2002	CCT (same group, repeated measure design)	Various types of cancer, 17	3	(1) Water humidification (2) aromatherapy with lavender (3) no treatment 60 min, one-off session 1 week	(1) and (2) showed a small reduction in blood pressure and pulse rate; decrease in pain, anxiety, depression scores; and an increase in overall wellbeing	Repeated lavender aromatherapy sessions might increase its benefits even more. No p-values provided
Maddocks-Jennings	RCT	Head and neck cancer patients, 19	3	(1) Essential oil gargle (manuka, kanuka mixture) (2) placebo gargle (3) standard care Gargling for at last 15 sec, 30 min before/after eating, drinking, smoking, radiotherapy From day of radiotherapy or 2 days before until 1 week after	(1) had delayed onset of mucositis (p=0.05) and reduced pain (no p-value) and oral symptoms (no p-value) compared to (2) and (3) (1) showed less weight loss (no p-value)	Small volumes of manuka and kanuka used in a gargle can provide positive effect on radiation-induced mucositis. Small sample size, few p-values provided
Soden, 2004	RCT	Various types of cancer, 42	3	Massages with (1) an essential oil and an inert carrier oil (2) an inert carrier oil only (3) no intervention	Sleep scores improved significantly in both groups (1) and (2) (P=0.02 and P=0.03); Reductions in depression scores in (2) (P=0.2)	Addition of lavender essential oil did not appear to increase the beneficial effects of massage

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				30 min weekly 1 month		
Stringer, 2008	RCT	Patients with haematological cancer, 39	3	(1) massage / light effleurage (stroking) moves (2) max of 3 aromatherapy oils with carrier oil, individualized (3) rest 20 min, one-off 24 hours	Significant difference between arms in cortisol (p=0.002) and prolactin (p=0.031) levels from baseline to 30 min post-session (1) had a significantly greater reduction in prolactin than (2), (3) (p=0.031) (1) and (2) showed significant improvement in EORTC QLQ-C30 (p=0.009)	In isolated haematological oncology patients, a significant reduction in cortisol could be safely achieved through aromatherapy, with associated improvement in psychological well-being
Wilcock, 2004	RCT	Various types of cancer, 46	2	(1) Aromatherapy massage and conventional day care (2) day care alone 30 min weekly for 4 weeks 1 month	No significant differences for mood, quality of life and intensity and bothersomeness of two main symptoms	Better set of outcome measures ought to be used for a larger RCT. Problem with retention of patients
Wilkinson, 1999	RCT	Various types of cancer, 103	2	(1) Aromatherapy massage (roman chamomile essential oil) (2) carrier oil massage "session" weekly for 3 weeks 1 ½ months	Improvements were found for each group measured with STAI-state ($p < 0.001$). Scores of group (1) improved on all RSCL subscales at the 1% level of significance or better: psychological ($p < 0.001$), quality of life ($p < 0.01$), severe physical ($p < 0.05$), and severe psychological ($P < 0.05$), except for severely restricted activities	Massage with or without essential oils appeared to reduce levels of anxiety. The addition of an essential oil seems to enhance the effect of massage and to improve physical and psychological symptoms, as well as overall quality of life
Wilkinson, 2007	RCT	Various types of cancer and clinical diagnosis of anxiety and/or depression, 288	2	(1) Aromatherapy massage (2) Standard care Weekly 1 hour massage for 4 weeks 2 ½ months	Group (1) showed significant improvement in clinical anxiety and/or depression compared with (2) at 6 weeks (P=0.1), but not at 10 weeks post randomization. (1) also described greater improvement in self-reported anxiety at both 6 and 10 weeks post-randomization (P=0.04 and P=0.04)	Aromatherapy massage did not appear to confer benefit on cancer patients' anxiety and/or depression in the long-term, but may be associated with clinically important benefit up to 2 weeks after the intervention

RCT – randomized clinical trial, CCT – clinical controlled trial, UCT – uncontrolled clinical trial

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Table 4: Results – preclinical studies

RefNo	Type of study	Focus of study	NA	Type of aromatherapy	Results	Conclusion
Anti-inflammatory activity						
45	in vitro study	to test the anti-inflammatory activities and effects of essential oils on neutrophil activation in vitro	NA	lemongrass, geranium and spearmint oils, amongst others	inhibitory activities for the neutrophil adherence were obtained by the major constituent terpenoids of citral, geraniol and carvone essential oils but not tea tree or lavender oil	
Anti-oxidant activity						
46	in vitro study	to test the antioxidant activity of the oil *Melissa officinalis* L. (lemon balm)	NA	*Melissa officinalis* L. (lemon balm)	oil was very effective against a series of human cancer cell lines	*Melissa officinalis* L. essential oil might be a potential anti-tumoral agent
Anti-cancer activity						
47	in vitro study	to assess the potentiating effect of beta-caryophyllene on the anticancer activity of alpha-humulene agianst human cancer cells	NA	isocaryophyllene (clove oil), *Humulus lupulus* (hops), hemp (*Cannabis sativa*), rosemary (*Rosmarinus officinalis*)	beta-caryophyllene promotes drug accumulation by a different mechanism of action and facilitates the passage of paclitaxel through the membrane	beta-caryophyllene potentiates its anticancer activity
Cytotoxicity						
48, 49	in vitro, mouse model	to assess cytotoxocity	NA	*Nigella sativa* L. (blackseed) and *Thymus broussonetti* (thyme)	essential oil showed significant in vitro cytotoxicity activity against tumor cells resistant to chemotherapy as well as a significant antitumor effect in mice	cytotoxicity of each extract depended on the tumor cell type
50	in vivo and in vitro	to assess cytotoxocity	NA	eucalyptol, carvacrol and thymol	Carvacrol and thymol significantly reduced the level of induced DNA damage	DNA-protective effects of carvacrol and thymol can be accompanied by their antioxidant action
Free radical scavenging activity						

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51	UCT	to examine the saliva of 22 human volunteers who had sniffed the aroma of lavender or rosemary	22	lavender, rosemary	free radical scavenging activity values were increased by stimulation with low concentrations of lavender or by high concentrations of rosemary both essential oil stimulations decreased cortisol levels	aromatherapy might have an effect on people by decreasing the stress hormone cortisol
Carcinogenesis / Carcinogen-metabolizing enzymes						
52	mouse model	to test the influence of essential oils on carcinogen-metabolizing enzymes and acid-soluble sulfhydryls	NA	cardamom, celery seed, cumin seed, coriander, ginger, nutmeg and zanthoxylium	only nutmeg and zanthoxylium oils induced cytochrome P450 level significantly cardamom oil caused a significant reduction in its activity aryl hydrocarbon hydroxylase activity was significantly elevated by treatment with ginger oil, whereas nutmeg oil caused a significant reduction in its activity	oral intake of essential oils seems to affect the host enzymes associated with activation and detoxication of xenobiotic compounds, including chemical carcinogens and mutagens
Apoptosis						
53	in vitro	to test morphological changes of classic apoptosis	NA	*Artemisia annul* L. (wormwood)	condensation of cytoplasm, fragmentation of nuclear chromatin, and apoptosis body was seen in cultured hepatocarcinoma cell SMMC-7721 (human hepatoma cell line)	Artemisia annul L. could indeed induce apoptosis of cultured SMMC-7721

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54	in vitro	to test for apoptosis	NA	*Curcuma wenyujin* (turmeric root)	was found to inhibit the growth of HepG2 cells in a dose-dependent manner and by inducing a cell cycle arrest in human HepG2 cancer cells	Curcuma wenyujin exhibits an anti-proliferative effect in HepG2 cells by inducing apoptosis
55	in vitro and in vivo		NA	*Zanthoxylum schinifolium* (prickly ash or Korean pepper)	decreased the cell viability and induced apoptotic death in HepG2 human hepatoma cells; in nude mice inoculated with Huh-7 human hepatoma cells, the extract significantly inhibited tumor development	potential candidate for hepatocellular carcinoma therapy
Chemo-preventative/antineoplastic						
56	in vivo	to test for chemo-preventive and therapeutic effects	NA	limonene	that limonene exhibits both chemo-preventive and therapeutic effects against chemically induced mammary tumors in rats	possible candidate for chemopreventative agent

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also found an increase in patient-identified symptom relief and psychological wellbeing. However, other trials did not report any significant difference between groups. Since the comparator interventions used in the included trials vary greatly, it was not possible to make an easy assessment regarding the system and component efficacy of specific essential oils. Although there were some RCT, the quality of publications ranges from mediocre to low. In particular, double-blinding as a quality marker of clinical trials is nearly impossible in trials in the field of aromatherapy, and thus study quality tends to be lower compared to conventional pharmacological trials. Moreover, adequate control interventions are needed. For example, massage therapy generally has a positive effect on the recipient and most positive effects discussed above stem from trials that in adjunction apply essential oils. Thus, it is difficult to be certain as to where exactly the reason for a positive effect lies. However, wellbeing and offering these effects in a package are of limited harm and thus some cancer clinics or other voluntary organizations now offer aromatherapy or aromatherapy massage free of charge or at a lower cost.

The cost of essential oils varies depending on the quality, i.e. what part of the plant the oil is extracted from and which method that was used to extract it. Oils may be purchased from a licensed aromatherapist. For instance, essential oil from rose petals retails at €100 per ounce (appr. 28 grams) - based on the 110 pounds (50 kg) of rose petals needed for a single ounce of essential oil. Other plants retail at much lower prices as they yield more essential oil (for instance lavender, lemon, and eucalyptus). Lavender can be bought at €22 per ounce. Treatments of aromatherapy usually are priced from €40 to €75 for a 90 minute session.

The number of theories that try to explain the mechanism of aromatherapy can be categorized into psychological aspects and neuro-chemical effects. Proposed mechanisms claim effects on the limbic and olfactory system, which in turn is suggested to have an effect on mood (Diego et al., 1998). However, only very limited research confirms effectiveness or mechanism of action and in-depth studies have yet to shed sufficient light on these possible mechanisms and the connection between the olfactory and limbic system. Proponents of essential oils / aromatherapy also believe that the effects these oils have on the body are greater than the sum of the individual components of the scents (Perry and Perry, 2006). Furthermore, there are various discussions amongst aromatherapists as to whether natural oils are superior to synthetic ones. Currently, there are no references to scientific studies of the issue.

Limitations

The limitations of this descriptive, systematic review include the fact that despite modern search engines and well-organized literature databases sometimes it is impossible to identify all the 'grey literature' regarding one topic. Thus, it is possible that the one or other study or case series is not included in this review. For instance, the medical search engine EMBASE was not searched. Furthermore, outcome measures and study designs of included studies varied to an extent that meta-analyzing the data was omitted due to heterogeneity.

As providers of essential oils are numerous and widespread in countries where aromatherapy is practiced, mainly on the European, North American, Australasian and Asian continents, comparability in trials with the same substance still may result in different outcomes. Moreover, training of aromatherapists and courses offered by some colleges and schools do not have a concerted curriculum which also includes a potential source of bias.

Conclusion

In summary, the use of diluted essential oils has minimal risks. Prolonged topical application may nevertheless cause allergic contact dermatitis. Repeated exposure to lavender and tea tree oils by topical administration was shown in one study to be associated with reversible prepubertal gynecomastia. Thus, patients with estrogen-dependant tumors should exercise caution. Aromatherapy/essential oils may be used safely by cancer patients for a short-term benefit in regard to reducing anxiety and depression symptoms and to increase sleep patterns and wellbeing.

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