# Phytotherapeutic Uses of Essential Oils

**Bob Harris**

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11.1 INTRODUCTION

For many, the term “aromatherapy” originally became associated with the concept of the holistic use of essential oils to promote health and well-being. As time has progressed and the psychophysical effects of essential oils have been explored further, their uses to reduce anxiety and aid sedation have also become associated with the term. This is especially so since the therapy has moved into the field of nursing, where such activities are of obvious benefit to patients in a hospital environment. More importantly, the practice of aromatherapy (in English-speaking countries) is firmly linked to the inhalation of small doses of essential oils and their application to the skin in high dilution as part of an aromatherapy massage.

This chapter is concerned with the medical use of essential oils, given to the patient by all routes of administration to treat specific conditions and in comparably concentrated amounts. Studies that use essential oils in an aromatherapy-like manner, for example, to treat anxiety by essential oil massage, are therefore excluded here.

Of the literature published in peer-reviewed journals over the last 30 years, only a small percentage concerns the administration of essential oils or their components to humans in order to treat disease processes. These reports are listed below in alphabetical order of their activity. The exception is the section on the respiratory tract, where the many activities of the two principal components (menthol and 1,8-cineole) are discussed and related to respiratory pathologies.

All of the references cited are from peer-reviewed publications; a minority is open to debate regarding methodology and/or interpretation of results, but this is not the purpose of this compilation. Reports of individual case studies have been omitted.

11.2 ACARICIDAL ACTIVITY

A number of essential oils have been found to have effective acaricidal activity against infections in the animal world. Recent examples include Origanum onites against cattle ticks (Coskun et al.,
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2008) and *Cinnamomum zeylanicum* against rabbit mange mites (Fichi et al., 2007). In comparison to veterinary research, there have been few investigations into human acaricidal infections.

The scabies mite, *Sarcoptes scabiei* var. *hominis*, is becoming increasingly resistant to existing acaricidal compounds such as lindane, benzyl benzoate, permethrin, and oral ivermectin. The potential use of a 5% *Melaleuca alternifolia* essential oil solution to treat scabies infections was investigated in vitro. It was found to be highly effective at reducing mite survival times and the main active component was terpinen-4-ol. However, the in vivo effectiveness was only tested on one individual, in combination with benzyl benzoate and ivermectin (Walton et al., 2004).

A double-blind, randomized, parallel group study was used to compare the effects of 25% w/w benzyl benzoate emulsion with 20% w/w *Lippia multiflora* essential oil emulsion in the treatment of scabies infection in 105 patients. Applied daily, the cure rates for the oil emulsion were 50%, 80%, and 80% for 3, 5, and 7 days, respectively, compared to 30%, 60%, and 70% for the benzyl benzoate emulsion. There were also less adverse reactions to the oil emulsion, leading it to be considered as an additional formulation for the treatment of scabies (Oladimeji et al., 2005).

Although not an infection, the lethal activity of essential oils toward the house dust mite (*Dermatophagoides farina* and *Dermatophagoides pteronyssinus*) is important as these mites are a major cause of respiratory allergies and an etiologic agent in the sensitization and triggering of asthma in children. Numerous studies have been conducted, including the successful inclusion of *Eucalyptus globulus* in blanket washing solutions (Tovey and McDonald, 1997), the high acaricidal activity of clove, rosemary, eucalyptus, and caraway (El-Zemity et al., 2006), and of tea tree and lavender (Williamson et al., 2007).

### 11.3 ANTICARCINOGENIC

Despite the popularity of in vitro experimentation concerning the cellular mechanisms of carcinogenic prevention by essential oil components (mainly by inducing apoptosis), there is no evidence that the direct administration of essential oils can cure cancer. There is evidence to suggest that the mevalonate pathway of cancer cells is sensitive to the inhibitory actions of dietary plant isoprenoids (e.g., Elson and Yu, 1994; Duncan et al., 2005). Animal testing has shown that some components can cause a significant reduction in the incidence of chemically induced cancers when administered before and during induction (e.g., Reddy et al., 1997; Uedo et al., 1999).

Phase II clinical trials have all involved perilyl alcohol. Results demonstrated that despite preclinical evidence, there appeared to be no anticarcinogenic activity in cases of advanced ovarian cancer (Bailey et al., 2002), metastatic colorectal cancer (Meadows et al., 2002), and metastatic breast cancer (Bailey et al., 2008). Only one trial has demonstrated antitumor activity as evidenced by a reduction of tumor size in patients with recurrent malignant gliomas (Orlando da Fonseca et al., 2008).

### 11.4 ANTIMICROBIAL

Considering that the majority of essential oil research is directed toward antimicrobial activity, there is a surprising lack of corresponding in vivo human trials. This is disappointing since the topical and systemic application of essential oils to treat infection is a widespread practice among therapists with (apparently) good results.

#### 11.4.1 ANTIBACTERIAL

Antibiotics that affect *Propionibacterium acnes* are a standard treatment for acne but antibiotic resistance is becoming prevalent. A preliminary study of 126 patients showed that topical 2% essential oil of *Ocimum gratissimum* (thymol chemotype) in a hydrophilic cream base was more effective than 10% benzyl peroxide lotion at reducing the number of lesions when applied twice daily for 4 weeks (Orafidiya et al., 2002).
In a randomized, single-blind, parallel-group-controlled trial, the same group examined the effects of the addition of aloe vera gel at varying concentrations to the *Ocimum gratissimum* cream and compared its activity with 1% clindamycin phosphate. In the 84 patients with significant acne, it was found that increasing the aloe gel content improved efficacy; the essential oil preparations formulated with undiluted or 50% aloe gels were more effective at reducing lesions than the reference product. The aloe vera gels alone had minimal activity (Orafidiya et al., 2004).

A later report judged the efficacy of a 5% *Melaleuca alternifolia* gel in the amelioration of mild to moderate acne, since a previous study (Raman et al., 1995) had demonstrated the effectiveness of tea tree oil components against *Propionibacterium acnes*. The randomized, double-blind, placebo-controlled trial used 60 patients who were given the tea tree oil gel or the gel alone twice daily for 45 days. The total acne lesion count was significantly reduced by 43.64% and the acne severity index was significantly reduced by 40.49% after the tea tree oil treatment, as compared to the placebo scores of 12.03% and 7.04%, respectively (Enshaieh et al., 2007).

### 11.4.1.1 Methicillin-Resistant *Staphylococcus aureus*

A number of papers have demonstrated the *in vitro* effects of various essential oils against methicillin-resistant *Staphylococcus aureus* (MRSA); for example, *Lippia origanoides* (Dos Santos et al., 2004), *Backhousia citriodora* (Hayes and Markovic, 2002), *Mentha piperita*, *Mentha arvensis*, and *Mentha spicata* (Imai et al., 2001), and *Melaleuca alternifolia* (Carson et al., 1995). There have been no trials involving the use of essential oils to combat active MRSA infections, although there have been two studies involving the use of tea tree oil as a topical decolonization agent for MRSA carriers.

A pilot study compared the use of 2% mupirocin nasal ointment and triclosan body wash (routine care) with 4% *Melaleuca alternifolia* essential oil nasal ointment and 5% tea tree oil body wash in 30 MRSA patients. The interventions lasted for a minimum of 3 days and screening for MRSA was undertaken at 48 and 96 h post-treatment from sites previously colonized by the bacteria. There was no correlation between length of treatment and outcome in either group. Of the tea tree oil group, 33% were initially cleared of MRSA carriage while 20% remained chronically infected at the end of the treatment; this was in comparison with routine care group of 13% and 53%, respectively. The trial was too small to provide significant results (Caelli et al., 2000).

A randomized, controlled trial compared the use of a standard regime for MRSA decolonization with *Melaleuca alternifolia* essential oil. The 5-day study involved 236 patients. The standard treatment group was given 2% mupirocin nasal ointment thrice daily, 4% chlorhexidine gluconate soap as a body wash once daily, and 1% silver sulfadiazine cream for skin lesions, wounds, and leg ulcers once daily. The tea tree oil group received 10% essential oil cream thrice daily to the nostrils and to specific skin sites and 5% essential oil body wash at least once daily. In the tea tree oil group, 41% were cleared of MRSA as compared to 49% using the standard regime; this was not a significant difference. Tea tree oil cream was significantly less effective at clearing nasal carriage than mupirocin (47% compared to 78%), but was more effective at clearing superficial sites than chlorhexidine or silver sulfadiazine (Dryden et al., 2004).

### 11.4.2 Antifungal

The essential oil of *Citrus aurantium* var. *amara* was used to treat 60 patients with tinea corporis, cruris, or pedis. One group received a 25% bitter orange (BO) oil emulsion thrice daily, a second group was treated with 20% bitter orange oil in alcohol (BOa) thrice daily, and a third group used undiluted BO oil once daily. The trial lasted for 4 weeks and clinical and mycological examinations were performed every week until cure, which was defined as an elimination of signs and symptoms. In the BO group, 80% of patients were cured in 1–2 weeks and the rest within 2–3 weeks. By using BOa, 50% of patients were cured in 1–2 weeks, 30% in 2–3 weeks, and 20% in 3–4 weeks. With the undiluted essential oil, 25% of patients did not continue treatment, 33.3% were cured in 1 week, 60% in 1–2 weeks, and 6.7% in 2–3 weeks (Ramadan et al., 1996).
A double-blind, randomized, placebo-controlled trial investigated the efficacy of 2% butenafine hydrochloride cream with added 5% *Melaleuca alternifolia* essential oil in 60 patients with toenail onychomycosis. After 16 weeks, 80% of patients in the treatment group were cured, as opposed to none in the control group (Syed et al., 1999). However, butenafine hydrochloride is a potent antimycotic in itself and the results were not compared with this product when used alone.

After an initial *in vitro* study, which showed that the essential oil of *Eucalyptus pauciflora* had a strong fungicidal activity against *Epidermophyton floccosum*, *Microsporum canis*, *Microsporum nanum*, *Microsporum gypseum*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton tonsurans*, and *Trichophyton violaceum*, an *in vivo* trial was commenced. Fifty patients with confirmed dermatophytosis were treated with 1% v/v essential oil twice daily for 3 weeks. At the end of the treatment, a cure was demonstrated in 60% of patients with the remaining 40% showing significant improvement (Shahi et al., 2000).

On the surmise that infection with *Pityrosporum ovale* is a major contributing factor to dandruff and that anti-*Pityrosporum* drugs such as nystatin were proven effective treatments, the use of 5% *Melaleuca alternifolia* essential oil was investigated. In this randomized, single-blind, parallel-group study tea tree oil shampoo or placebo shampoo was used daily for 4 weeks by 126 patients with mild to moderate dandruff. In the treatment group, the dandruff severity score showed an improvement of 41%, as compared to 11% in the placebo group. The area involvement and total severity scores also demonstrated a statistically significant improvement, as did itchiness and greasiness. Scaliness was not greatly affected. The condition resolved for one patient in each group and so ongoing application of tea tree oil shampoo was recommended for dandruff control (Satchell et al., 2002a).

For inclusion in a randomized, double-blind, controlled trial, 158 patients with the clinical features of intertriginous tinea pedis and confirmed dermatophyte infection were recruited. They were administered 25% or 50% *Melaleuca alternifolia* essential oil (in an ethanol and polyethylene glycol vehicle) or the vehicle alone, twice daily for 4 weeks. There was an improvement in the clinical severity score, falling by 68% and 66% in the 25% and 50% tea tree oil groups, in comparison with 41% for the placebo. There was an effective cure in the 25% and 50% tea tree oil and placebo groups of 48%, 50%, and 13%, respectively. The essential oil was less effective than standard topical treatments (Satchell et al., 2002b).

The anticandida properties of *Zataria multiflora* essential oil and its active components (thymol, carvacrol, and eugenol) were demonstrated *in vitro* by Mahmoudabadi et al. (2006). A randomized, clinical trial was conducted using 86 patients with acute vaginal candidiasis. They were treated with a cream containing 0.1% *Zataria multiflora* essential oil or 1% clotrimazole once daily for 7 days. Statistically significant decreases in vulvar pruritis (80.9%), vaginal pruritis (65.5%), vaginal burning (73.95), urinary burning (100%), and vaginal secretions (90%) were obtained by the essential oil treatment as compared to the clotrimazole treatment of 73.91%, 56.7%, 82.1%, 100%, and 70%, respectively. In addition, the *Zataria multiflora* cream reduced erythema and satellite vulvar lesions in 100% of patients, vaginal edema in 100%, vaginal edema in 83.3%, and vulvo-vaginal excoriation and fissures in 92%. The corresponding results for clotrimazole were 100%, 100%, 76%, and 88%. In terms of overall efficacy, the rates of improvement were 90% and 74.8% for the *Zataria multiflora* and clotrimazole groups, respectively. Use of the cream alone provided no significant changes (Khosravi et al., 2008).

**11.4.3 Antiviral**

The *in vitro* studies that have been conducted so far indicate that many essential oils possess antiviral properties, but they affect only enveloped viruses and only when they are in the free state, that is, before the virus is attached to, or has entered the host cell (e.g., Schnitzler et al., 2008). This is in contrast to the majority of synthetic antiviral agents, which either bar the complete penetration of viral particles into the host cell or interfere with viral replication once the virus is inside the cell.
A randomized, investigator-blinded, placebo-controlled trial used 6% *Melaleuca alternifolia* essential oil gel to treat recurrent herpes labialis. It was applied five times daily and continued until re-epithelialization occurred and the polymerase chain reaction (PCR) for Herpes simplex virus was negative for two consecutive days. The median time to re-epithelialization after treatment with tea tree oil was 9 days as compared to 12.5 days with the placebo, which is similar to reductions caused by other topical therapies. The median duration of PCR positivity was the same for both groups (6 days) although the viral titers appeared slightly lower in the oil group on days 3 and 4. None of the differences reached statistical significance, probably due to the small group size (Carson et al., 2001).

Children below 5 years were enrolled in a randomized trial to test a 10% v/v solution of the essential oil of *Backhousia citriodora* against molluscum contagiosum (caused by Molluscipox-virus). Of the 31 patients, 16 were assigned to the treatment group and the rest to the control of olive oil. The solutions were applied directly to the papules once daily at bedtime for 21 days or until the lesions had resolved. In the essential oil group, five children had a total resolution of lesions and four had reductions of greater than 90% at the end of 21 days. In contrast, none of the control group had any resolution or reduction of lesions by the end of the study period (Burke et al., 2004).

A study was conducted on 60 patients who were chronic carriers of hepatitis B or C. The essential oils of *Cinnamomum camphora* ct 1,8-cineole, *Daucus carota*, *Ledum groelandicum*, *Laurus nobilis*, *Helichrysum italicum*, *Thymus vulgaris* ct thujanol, and *Melaleuca quinquenervia* were used orally in various combinations. They were used as a monotherapy or as a complement to allopathic treatment. The objectives of treatment were normalization of transaminase levels, reduction of viral load, and stabilization or regression of fibrosis. There was an improvement of 100%, when patients with hepatitis C were given bitherapy with essential oils. With essential oil monotherapy, improvements were noted in 64% of patients with hepatitis C and there were two cures of hepatitis B (Giraud-Robert, 2005).

### 11.4.4 Microbes of the Oral Cavity

The activities of essential oils against disease-producing microbes in the oral cavity have been documented separately because there are numerous reports of relevance. The easy administration of essential oils in mouthrinses, gargles, and toothpastes, and the success of such commercial preparations, has no doubt led to the popularity of this research.

The *in vitro* activities of essential oils against the oral microflora are well documented and these include effects on cariogenic and periodontopathic bacteria. One example is the *in vitro* activity of *Leptospermum scoparium*, *Melaleuca alternifolia*, *Eucalyptus radiata*, *Lavandula officinalis*, and *Rosmarinus officinalis* against *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, *Fusobacterium nucleatum*, and *Streptococcus mutans*. The essential oils inhibited all of the test bacteria, acting bactericidally except for *Lavandula officinalis*. In addition, significant adhesion-inhibiting activity was shown against *Streptococcus mutans* by all essential oils and against *Porphyromonas gingivalis* by tea tree and manuka (Takarada et al., 2004).

There have been at least six *in vivo* studies concerning the activity of individual essential oils against the microflora of the oral cavity. In addition, a review of the literature finds a surprising number of *in vivo* papers that detail the activities of “an essential oil mouthrinse.” Closer examination reveals that the essential oil mouthrinse is the commercial product, Listerine. Although Listerine contains 21% or 26% alcohol (depending on the exact product), a 6-month study has shown that it contributes nothing to the efficaciousness of the mouthrinse (Lamster et al., 1983). The active ingredients are 1,8-cineole (0.092%), menthol (0.042%), methyl salicylate (0.06%), and thymol (0.64%). For this reason, a small random selection of such papers is included below.
11.4.4.1 Activity of Listerine against Plaque and/or Gingivitis

An observer-blind, 4-day plaque regrowth, crossover study compared the use of Listerine® with a triclosan mouthrinse and two placebo controls in 32 volunteers. All normal hygiene procedures were suspended except for the rinses. The triclosan product produced a 45% reduction in plaque area and a 12% reduction in plaque index against its placebo, in comparison with 52% and 17%, respectively, for the essential oil rinse. The latter was thus deemed more effective (Moran et al., 1997).

A similar protocol was used to compare the effects of Listerine against an amine fluoride/stannous fluoride-containing mouthrinse (Meridol®) and a 0.1% chlorhexidine mouthrinse (Chlorhexamed®) in inhibiting the development of supragingival plaque. On day 5 of each treatment, the results from 23 volunteers were evaluated. In comparison with their placebos, the median plaque reductions were 12.2%, 23%, and 38.2% for the fluoride, essential oil, and chlorhexidine rinses, respectively. The latter two results were statistically significant (Riep et al., 1999).

After the assessment for the presence of gingivitis and target pathogens (Porphyromonas gingivalis, Fusobacterium nucleatum, and Veillonella sp.) and total anaerobes, 37 patients undertook a twice daily mouthrinse with Listerine for 14 days. After a washout period, the study was conducted again using a flavored hydroalcoholic placebo. The results of this randomized, double-blind, crossover study showed that the essential oil rinse significantly lowered the number of all target pathogens by 66.3–79.2%, as compared to the control (Fine et al., 2007).

The effect of adding Listerine mouthrinse to a standard oral hygiene regime in 50 orthodontic patients was examined. The control group brushed and flossed twice daily, whereas the test group also used the mouthrinse twice daily. Measurements of bleeding, gingival, and plaque indices were conducted at 3 and 6 months. All three indices were significantly lowered in the test group as compared to the control at both time intervals (Tufekci et al., 2008).

The same fixed combination of essential oils that is found in Listerine mouthrinse has been incorporated into a dentifrice. Such a dentifrice was used in a 6-month double-blind study to determine its effect on the microbial composition of dental plaque as compared to an identical dentifrice without essential oils. Supragingival plaque and saliva samples were collected at baseline and their microbial content characterized, after which the study was conducted for 6 months. The essential oil dentifrice did not significantly alter the microbial flora and opportunistic pathogens did not emerge, nor was there any sign of developing resistance to the essential oils in tested bacterial species (Charles et al., 2000).

The same dentifrice was examined for antiplaque and antigingivitis properties in a blinded, randomized, controlled trial. Before treatment, 200 patients were assessed using a plaque index, a modified gingival index (GI), and a bleeding index. The dentifrice was used for 6 months, after which another assessment was made. It was found that the essential oil dentifrice had a statistically significant lower whole-mouth and interproximal plaque index (18.3% and 18.1%), mean GI (16.2% and 15.5%), and mean bleeding index (40.5% and 46.9%), as compared to the control. It was therefore proven to be an effective antiplaque and antigingivitis agent (Coelho et al., 2000).

11.4.4.2 Antiviral Listerine

A trial was conducted to examine whether a mouthrinse could decrease the risk of viral crosscontamination from oral fluids during dental procedures. Forty patients with a perioral outbreak of recurrent herpes labialis were given a 30-s mouthrinse with either water or Listerine. Salivary samples were taken at baseline, immediately following the rinse and 30 min after the rinse and evaluated for the viral titer. Infectious virions were reduced immediately to zero postrinse and there was a continued significant reduction 30 min postrinse. The reduction by the control was not significant (Meiller et al., 2005).

11.4.4.3 Activity of Essential Oils

The antibacterial activity of the essential oil of Lippia multiflora was first examined in vitro for antimicrobial activity against ATCC strains and clinical isolates of the buccal flora. A significant
activity was found, with an MBC of 1/1400 for streptococci and staphylococci, 1/800 for enterobacteria and neisseria, and 1/600 for candida. A mouthwash was prepared with the essential oil at a 1/500 dilution and this was used in two clinical trials.

The buccodental conditions of 26 French children were documented by measuring the percentage of dental surface free of plaque, gum inflammation, and the papillary bleeding index (PBI). After 7 days of rinsing with the mouthwash for 2 min, the test group was found to have a reduction of dental plaque in 69% of cases and a drop in PBI with a clear improvement of gum inflammation in all cases. The second trial was conducted in the Cote d’Ivoire with 60 adult patients with a variety of conditions. After using the mouthwash after every meal for 5 days, it was found that candidiasis had disappeared in most cases, gingivitis was resolved in all patients, and 77% of dental abscesses had resolved (Pélissier et al., 1994).

Fluconazole-refractory oropharyngeal candidiasis is a common condition in HIV patients. Twelve such patients were treated with 15 mL of a *Melaleuca alternifolia* oral solution (Breath-Away) four times daily for 2 weeks, in a single center, open-label clinical trial. The solution was swished in the mouth for 30–60 s and then expelled, with no rinsing for at least 30 min. Clinical assessment was carried out on days 7 and 14 and also on days 28 and 42 of the follow-up. Two patients were clinically cured and six were improved after the therapy; four remained unchanged and one deteriorated. The overall clinical response rate was thus 67% and was considered as a possible alternative antifungal treatment in such cases (Jandourek et al., 1998).

A clinical pilot study compared the effect of 0.34% *Melaleuca alternifolia* essential oil solution with 0.1% chlorhexidine on supragingival plaque formation and vitality. Eight subjects participated, with a 10-day washout period between each treatment regime of 1 week. The plaque area was calculated using a stain and plaque vitality was estimated using a fluorescence technique. Neither of these parameters was reduced by the tea tree oil treatment (Arweiler et al., 2000).

A gel containing 2.5% *Melaleuca alternifolia* essential oil was used in a double-blind, longitudinal noncrossover trial and compared with a chlorhexidine gel positive control and a placebo gel in the treatment of plaque and chronic gingivitis. The gels were applied as a dentifrice twice daily by 49 subjects for 8 weeks and the treatment was assessed using a gingival index (GI), a PBI, and a plaque staining score. The tea tree group showed a significant reduction in PBI and GI scores, although plaque scores were not reduced. It was apparent that the tea tree gel decreased the level of gingival inflammation more than the positive or negative controls (Soukoulis and Hirsch, 2004).

A mouthcare solution consisting of an essential oil mixture of *Melaleuca alternifolia*, *Mentha piperita*, and *Citrus limon* in a 2:1:2 ratio diluted in water to a 0.125% solution was used to treat oral malodor in 32 intensive care unit patients, 13 of whom were ventilated. The solution was used to clean the teeth, tongue, and oral cavity twice daily. The level of malodor was assessed by a nurse using a visual analogue scale, and volatile sulfur compounds (VSC) were measured via a probe in the mouth, before, 5 and 60 min after treatment. On the second day, the procedure was repeated using benzydamine hydrochloride (BH), which is normally used for oral hygiene, instead of essential oil solution. The perception of oral malodor was significantly lowered after the essential oil treatment but not after the BH treatment. There was a decrease in VSC levels at 60 min for both treatment groups, but not after 5 min for the oil mixture. The results suggested that just one session with the essential oil mixture could improve oral malodor and VSC in intensive care patients (Hur et al., 2007).

The essential oil of *Lippia sidoides* (rich in thymol and carvacrol) was used in a double-blind, randomized, parallel-armed study against gingival inflammation and bacterial plaque. Fifty-five patients used a 1% essential oil solution as a mouthrinse twice daily for 7 days and the results were compared with a positive control, 0.12% chlorhexidine. Clinical assessment demonstrated decreased plaque index and gingival bleeding scores as compared to the baseline, with no significant difference between test and control. The essential oil of *Lippia sidoides* was considered a safe and effective treatment (Botelho et al., 2007).
11.4.5 CONTROLLING MICROFLORA IN ATOPIC DERMATITIS

Rarely found on healthy skin, *Staphylococcus aureus* is usually present in dry skin and is one of the factors that can worsen atopic dermatitis. Toxins and enzymes deriving from this bacteria cause skin damage and form a biofilm from fibrin and glyocalyx, which aids adhesion to the skin and resistance to antibiotics. An initial *in vitro* study found that a mixture of xylitol (a sugar alcohol) and farnesol was an effective agent against *Staphylococcus aureus*; xylitol inhibited the formation of glyocalyx whereas farnesol dissolved fibrin and suppressed *Staphylococcus aureus* growth without affecting *Staphylococcus epidermidis* (Masako et al., 2005a).

The same mixture of xylitol and farnesol was used in a double-blind, randomized, placebo-controlled study of 17 patients with mild to moderate atopic dermatitis on their arms. A skin-care cream containing 0.02% farnesol and 5% xylitol or the cream alone was applied to either the left or the right arms for 7 days. The ratio of *Staphylococcus aureus* to other aerobic skin microflora was significantly decreased in the test group compared to placebo, from 74% to 41%, while the numbers of coagulase-negative staphylococci increased. In addition, skin conductance (indicating hydration of skin surface) significantly increased at the test cream sites compared to before application and to the placebo (Masako et al., 2005b).

11.4.6 ODOR MANAGEMENT FOR FUNGATING WOUNDS

Fungating wounds may be caused by primary skin carcinomas, underlying tumors or via spread from other tissues. The malodor associated with such necrosis is caused by the presence of aerobic and anaerobic bacteria. The wounds rarely heal and require constant palliative treatment, leading to social isolation of the patients and poor quality of life.

Smell reduction with essential oils was first reported by Warnke et al. (2004) in 25 malodorous patients with inoperable squamous cell carcinoma of the head and neck. A commercial product containing eucalyptus, grapefruit, and tea tree essential oils (Megabac®) was applied topically to the wounds twice daily. Normal medication apart from Betadine disinfection was continued. The smell disappeared completely within 2–3 days and signs of superinfection and pus secretion were reduced in the necrotic areas.

Megabac has also been used in a small pilot study (10 patients) to treat gangrenous areas, being applied via spray thrice daily until granulation tissue formed. The treatment was then continued onto newly formed split skin grafts. All wounds healed within 8 weeks and no concurrent antibiotics were used (Sherry et al., 2003).

Use of essential oils to reduce the smell of fungating wounds in 13 palliative care patients was detailed by another group the following year. *Lavandula angustifolia, Melaleuca alternifolia,* and *Pogostemon cablin* essential oils were used alone or in combinations at 2.5–5% concentrations in a cream base. The treatments were effective (Mercier and Knevitt, 2005).

A further study was conducted with 30 patients suffering incurable head and neck cancers with malodorous necrotic ulcers. A custom-made product (Klonemax®) containing eucalyptus, tea tree, lemongrass, lemon, clove, and thyme essential oils was applied topically (5 mL) twice daily. All patients had a complete resolution of the malodor; in addition to the antibacterial activity, an anti-inflammatory effect was also noted (Warnke et al., 2006).

The use of essential oils to treat malodorous wounds in cancer patients is becoming widespread in many palliative care units although no formal clinical trials have been conducted as yet.

11.5 DISSOLUTION OF HEPATIC AND RENAL STONES

11.5.1 GALL AND BILIARY TRACT STONES

Rowachol and Rowatinex are two commercial products that have been marketed for many years and are based on essential oil components. They are sometimes thought of as being the same product but
in fact they are different. The compositions have changed slightly over the years and the most recently disclosed are shown in Table 11.1.

Rowachol has been in use for over 50 years for the dissolution of gallstones and biliary tract stones. There have been many published works on its effects and at least one double-blind trial (Lamy, 1967). It has been stated that although the dissolution rate of Rowachol is not impressive, it is still much greater than Rowatinex and could occur spontaneously (Doran and Bell, 1979). It has been employed alone as a useful therapy for common duct stones (Ellis and Bell, 1981) although improved results were demonstrated when Rowachol was used in conjunction with bile acid therapy (Ellis et al., 1981).

Rowachol has been shown to inhibit hepatic cholesterol synthesis mediated by a decreased hepatic S-3-hydroxy-3-methylglutaryl-CoA reductase activity (Middleton and Hui, 1982); the components mostly responsible for this activity were menthol and 1,8-cineole, with pinene and camphene having no significant effect (Clegg et al., 1980). A reduction in cholesterol crystal formation in the bile of gallstone patients has been demonstrated in a small trial using Rowachol (von Bergmann, 1987).

Two early uncontrolled trials reported that Rowachol significantly increased plasma high-density lipoprotein (HDL) cholesterol when administered to patients with low HDL cholesterol; a twofold increase was found in 10 subjects after 6 weeks of treatment (Hordinsky and Hordinsky, 1979), while a progressive increase in HDL of 14 subjects was noted, >100% after 6 months (Bell et al., 1980). This was interesting as low plasma concentrations of HDLs are associated with an elevated risk of coronary heart disease. However, a double-blind, placebo-controlled trial that administered six capsules of Rowachol daily for 24 weeks to 19 men found that there were no significant HDL-elevating effects of the treatment (Cooke et al., 1998). It is currently thought that monoterpenes have no HDL-elevating potential that is useful for disease prevention.

In vitro, a solution of 97% d-limonene was found to be 100-fold better at solubilizing cholesterol than sodium cholate. A small trial followed with 15 patients, whereby 20 ml of the d-limonene preparation was introduced into the gallbladder via a catheter on alternate days for up to 48 days. The treatment was successful in 13 patients with gallstone dissolution sometimes occurring after three infusions. Side effects included vomiting and diarrhea (Igimi et al., 1976).

A further study was conducted by Igimi et al. (1991) using the same technique with 200 patients. Treatments lasted from 3 weeks to 4 months. Complete or partial dissolution of gallstones was achieved in 141 patients, with complete disappearance of stones in 48% of cases. Epigastric pain was experienced by 168 patients and 121 suffered nausea and vomiting. Further trials have not been conducted.
11.5.2 Renal Stones

While Rowachol is used as a measure against gallstones and biliary tract stones, Rowatinex is used in the treatment of renal stones. The first double-blind, randomized trial was conducted by Mukamel et al. (1987) on 40 patients with acute renal colic. In the Rowatinex group, there was a significantly higher expulsion rate of stones ≥3 mm in diameter in comparison with the placebo (61% and 28%, respectively). There was also a higher overall success rate in terms of spontaneous stone expulsion and/or disappearance of ureteral dilatation in the treatment group compared to placebo (78–52%), but the difference was not statistically significant.

A second double-blind, randomized trial was conducted on 87 patients with ureterolithiasis. Four Rowatinex capsules were prescribed four times a day, the average treatment time being two weeks. The overall stone expulsion rate was significantly higher in the Rowatinex group as compared to placebo; 81% and 51%, respectively. Mild to moderate gastrointestinal disturbances were noted in seven patients. It was concluded that the early treatment of ureteral stones with Rowatinex was preferable before more aggressive measures were considered (Engelstein et al., 1992).

Rowatinex has also been used with success in the removal of residual stone fragments after extracorporeal shock wave lithotripsy, a situation that occurs in up to 72% of patients when given this therapy. With 50 patients, it was found that Rowatinex decreased the number of calculi debris, reducing the number of late complications and further interventions. By day 28, 82% of patients were free of calculi whereas this situation is normally reached after 3 months without Rowatinex treatment (Siller et al., 1998).

A minor study examined the use of Rowatinex in the management of childhood urolithiasis. Six children aged from 4 months to 5 years were administered varying doses of the preparation from 10 days to 12 weeks. All patients became stone-free with no side effects, although a definite conclusion as to the efficacy of treatment could not be established due to the small patient number involved (Al-Mosawi, 2005).

A comparison of the effects of an α-blocker (tamsulosin) and Rowatinex for the spontaneous expulsion of ureter stones and pain control was undertaken using 192 patients. They were divided into three groups: analgesics only, Rowatinex with analgesics, and tamsulosin with analgesics. For ureter stones less than 4 mm in diameter, their excretion was accelerated by both Rowatinex and tamsulosin. The use of these two treatments also decreased the amount of analgesics required and it was concluded that they should be considered as adjuvant regimes (Bak et al., 2007).

11.6 Functional Dyspepsia

Several essential oils have been used in the treatment of functional (nonulcer) dyspepsia. All of the published trials have concerned the commercial preparation known as Enteroplant®, an enteric-coated capsule containing 90 mg of Mentha × piperita, and 50 mg of Carum carvi essential oils.

The combination of peppermint and caraway essential oils has been shown to act locally in the gut as an antispasmodic (Micklefield et al., 2000, 2003) and to have a relaxing effect on the gallbladder (Goerg and Spilker, 2003). The antispasmodic effect of peppermint is well documented and that of caraway essential oil has also been demonstrated (Reiter and Brandt, 1985). The latter alone has also been shown to inhibit gallbladder contractions in healthy volunteers, increasing gallbladder volume by 90% (Goerg and Spilker, 1996).

One of the first studies involved 45 patients in a double-blind, placebo-controlled multicenter trial with the administration of Enteroplant thrice daily for 4 weeks. It was found to be superior to placebo with regard to pain frequency, severity, efficacy, and medical prognosis. Clinical Global Impressions were improved for 94.5% of patients using the essential oil combination (May et al., 1996).

The activity of Enteroplant (twice daily) was compared with that of cisapride (30 mg daily), a serotonin 5-HT₄ agonist that stimulates upper gastrointestinal tract motility, over a 4-week period.
This double-blind, randomized trial found that both products had comparable efficacy in terms of pain severity and frequency, Dyspeptic Discomfort Score, and Clinical Global Impressions (Madisch et al., 1999).

Another double-blind, randomized trial administered either Enteroplant or placebo twice daily for 28 days. Pain intensity and pressure, heaviness, and fullness were reduced in the test group by 40% and 43% as compared to 22% for both in the placebo group, respectively. In addition, Clinical Global Impressions were improved by 67% for the peppermint/caraway combination whereas the placebo scored 21% (May et al., 2000).

Holtmann et al. (2001) were the first to investigate the effect of Enteroplant (twice daily) on disease-specific quality of life as measured by the Nepean Dyspepsia Index. All scores were significantly improved compared to the placebo. In 2002, the same team also demonstrated that patients suffering with severe pain or severe discomfort both responded significantly better in comparison with the placebo.

Approximately 50% of patients suffering from functional dyspepsia are infected with *Helicobacter pylori* (Freidman, 1998). The *Helicobacter* status of 96 patients and the efficacy of Enteroplant were compared by May et al. (2003). They found that patients with *Helicobacter pylori* infection demonstrated a substantially better treatment response than those who were not infected. However, a previous study found no efficacy differences between infected and noninfected functional dyspepsia patients (Madisch et al., 2000) and so the effect of the presence of the bacterium on Enteroplant treatment has yet to be elucidated.

A short review of the literature concluded that treatment with the fixed peppermint/caraway essential oil combination had demonstrated significant efficacy in placebo-controlled trials, had good tolerability and safety, and could thus be considered for the long-term management of functional dyspepsia patients (Holtmann et al., 2003).

11.7 GASTROESOPHAGEAL REFLUX

*d*-Limonene has been found to be effective in the treatment of gastroesophageal reflux disorder. Nineteen patients took one capsule of 1000 mg *d*-limonene every day and rated their symptoms using a severity/frequency index. After 2 days, 32% of patients had significant relief and by day 14, 89% of patients had complete relief of symptoms (Wilkins, 2002).

A double-blind, placebo-controlled trial was conducted with 13 patients who were administered one 1000 mg capsule of *d*-limonene daily or on alternate days. By day 14, 86% of patients were asymptomatic compared to 29% in the placebo group (Wilkins, 2002).

The mechanism of action of *d*-limonene has not been fully elucidated in this regard but it is thought that it may coat the mucosal lining and offer protection against gastric acid and/or promote healthy peristalsis.

11.8 HYPERLIPOPROTEINEMIA

Girosital is a Bulgarian encapsulated product consisting of rose essential oil (68 mg) and vitamin A in sunflower vegetable oil. Initial animal studies found that rose oil administered at 0.01 and 0.05 mL/kg had a hepatoprotective effect against ethanol. Dystrophy and lipid infiltration were lowered and glycogen tended to complete recovery, suggesting a beneficial effect of rose oil on lipid metabolism (Kirov et al., 1988a).

Girosital was administered to 33 men with long-standing alcohol abuse, twice daily for 3 months. It significantly reduced serum triglycerides and low-density lipoprotein and increased the level of HDL-cholesterin; it was particularly effective for the treatment of hyperlipoproteinemia types IIb and IV. Liver lesions relating to alcohol intoxication improved and subjective complaints such as dyspeptic symptoms and pain were reduced (Konstantinova et al., 1988).
The hypolipidemic effect of Girosital was again studied by giving a capsule once daily for 20 days in 35 patients with hyperlipoproteinemia. In type IIa hyperlipoproteinemia cases, the total lipids were reduced by 23.91% and the total cholesterol by 10.64%. For type IIb patients, the total lipid reduction was 15.93%, triglycerides fell by 25.45%, and cholesterol by 14.06%; in type IV cases the reductions were 33.83%, 25.33%, and 36%, respectively. Girosital was more effective in comparison with the treatment with bezalipe and clofibrate (Stankusheva, 1988).

Thirty-two patients with hyperlipoproteinemia and arterial hypertension were administered one Girosital capsule twice daily for 110 days. A marked reduction in hyperlipoproteinemia was demonstrated in all patients. The hypocholesterolemic effect manifested first in type IIa patients after 20 days, and later in type IIb cases. Reduction of serum triglycerides in type IIb began 50 days after the commencement of treatment (Kirov et al., 1988b).

A further study (Mechkov et al., 1988) examined the effect of Girosital capsules twice daily for 110 days in 30 patients with cholelithiasis, liver steatosis, and hyperlipoproteinemia. Total cholesterol decreased after 20 days of treatment although it tended to rise slightly later in the test period. The triglycerides were most affected in hyperlipoproteinemia types IIb and IV. The \(\beta\)-lipoprotein values were not altered by the treatment.

### 11.9 Irritable Bowel Syndrome

The essential oil of *Mentha x piperita* has been used for many years as a natural carminative of the gastrointestinal tract. This effect is principally due to the antispasmodic activity of menthol, which acts as a calcium channel antagonist of the intestinal smooth muscle (Taylor et al., 1984, 1985). Secondary effects include a reduction of gastrointestinal foam by peppermint oil (Harries et al., 1978) and a choleretic activity that is attributed to menthol (Rangelov et al., 1988). The reduction of intestinal hydrogen production caused by bacterial overgrowth has also been demonstrated in patients by enteric-coated peppermint oil (Logan and Beaulne, 2002).

The first clinical trial of peppermint for the treatment of irritable bowel syndrome was conducted by Rees et al. (1979). They prescribed 0.2 mL of peppermint oil in enteric-coated capsules (1–2 capsules depending on symptom severity) thrice daily. Patient assessment considered the oil to be superior to the placebo in relieving abdominal symptoms. Since then, a further 15 double-blind and two open trials have been conducted; examples of these can be seen in Table 11.2.

Eight studies used the commercial preparation known as Colpermin® and two used Mintoil®, the capsules of which contain 187 and 225 mg of peppermint oil, respectively. The other studies used enteric-coated capsules usually containing 0.2 mL of the essential oil.

The latest trial (Cappello et al., 2007) used a randomized, double-blind, placebo-controlled design to test the efficacy of two capsules of Mintoil twice daily for 4 weeks. The symptoms evaluated before the treatment and at 4 and 8 weeks post-treatment were abdominal bloating, pain or discomfort, diarrhea, constipation, incomplete or urgency of defecation, and the passage of gas or mucus. The frequency and intensity of these symptoms was used to calculate the total irritable bowel syndrome symptoms score. At 4 weeks, 75% of patients in the peppermint oil group demonstrated a >50% reduction of the symptoms score as compared to 38% in the placebo group. At 4 and 8 weeks in the peppermint oil group compared to that before the treatment, there was a statistically significant reduction of the total irritable bowel syndrome symptoms score whereas there was no change with the placebo.

A critical review and meta-analysis of the use of peppermint oil for irritable bowel syndrome was published by Pittler and Ernst (1998). They examined five double-blind, placebo-controlled trials; there was a significant difference between peppermint oil and placebo in three cases and no significant difference in two cases. It was concluded that although a beneficial effect of peppermint oil was demonstrated, its role in treatment was not established.
A review of 16 trials was conducted by Grigoleit and Grigoleit (2005). They concluded that there was reasonable evidence that the administration of enteric-coated peppermint oil (180–200 mg) thrice daily was an effective treatment for irritable bowel syndrome when compared to placebo or the antispasmodic drugs investigated (mebeverine, hyoscyamine, and alverine citrate).

A comparison between two commercial delayed release peppermint oil preparations found that there were differences in the pharmacokinetics in relation to bioavailability times and release site. A capsule that is more effective in delivering the peppermint oil to the distal small intestine and ascending colon would be more beneficial in the treatment of irritable bowel syndrome (White et al., 1987). It has also been suggested that the conflicting results in some trials may be due to the inclusion of patients suffering from lactose intolerance, syndrome of small intestinal bacterial overgrowth, and celiac disease, all of which have symptoms similar to irritable bowel disease (Cappello et al., 2007).

### 11.10 MEDICAL EXAMINATIONS

Although not employed in a treatment context, the antispasmodic activity of peppermint essential oil has been used to facilitate examinations of the upper and lower gastrointestinal tract. A few examples are highlighted below.

Peppermint oil has also been used during double-contrast barium enemas. The study comprised 383 patients in four groups, two being no-treatment and Buscopan groups. The preparation, consisting of 8 mL of essential oil, 0.2 mL of Tween 80 in 100 mL water, was administered in 30 mL quantities via the enema tube or mixed in with the barium meal. Peppermint oil had the same spasmylytic effect as systemic Buscopan in the transverse and descending colon and a stronger effect in the cecum and ascending colon. Both methods of peppermint oil administration were equally effective (Asao et al., 2003).

### TABLE 11.2
Examples of Clinical Trials of Peppermint Oil in the Treatment of Irritable Bowel Syndrome

<table>
<thead>
<tr>
<th>Patients</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>0.2–0.4 mL thrice daily for 3 weeks</td>
<td>Superior to placebo in relieving abdominal symptoms</td>
<td>Rees et al. (1979)</td>
</tr>
<tr>
<td>29</td>
<td>0.2–0.4 mL thrice daily for 2 weeks</td>
<td>Superior to placebo in relieving abdominal symptoms</td>
<td>Dew et al. (1984)</td>
</tr>
<tr>
<td>25</td>
<td>0.2 mL thrice daily for 2 weeks</td>
<td>No significant change in symptoms as compared to placebo</td>
<td>Lawson et al. (1988)</td>
</tr>
<tr>
<td>35</td>
<td>One Colpermin thrice daily for 24 weeks</td>
<td>Effective in relieving symptoms</td>
<td>Shaw et al. (1991)</td>
</tr>
<tr>
<td>110</td>
<td>One Colpermin 3–4 times daily for 2 weeks</td>
<td>Significant improvement in symptoms as compared to placebo</td>
<td>Liu et al. (1997)</td>
</tr>
<tr>
<td>42</td>
<td>1–2 Colpermin thrice daily for 2 weeks</td>
<td>75% of children had reduced pain severity</td>
<td>Kline et al. (2001)</td>
</tr>
<tr>
<td>178</td>
<td>Two Mintoil thrice daily for 3 months</td>
<td>Significant improvement in gastroenteric symptoms as compared to placebo (97% versus 33%, respectively)</td>
<td>Capanni et al. (2005)</td>
</tr>
<tr>
<td>57</td>
<td>Two Mintoil twice daily for 4 weeks</td>
<td>Significant reduction in overall symptom score</td>
<td>Cappello et al. (2007)</td>
</tr>
</tbody>
</table>
Orally administered peppermint oil was used in a randomized trial in 430 patients undergoing a double-contrast barium meal examination, without other antispasmodics. A reduction in spasms of the esophagus, lower stomach, and duodenal bulb was found, along with an inhibition of barium flow to the distal duodenum and an improvement of diagnostic quality (Shigeaki et al., 2006).

During endoscopic retrograde cholangiopancreatography, Buscopan or glucagon is used to inhibit duodenal motility but produce adverse effects. Various concentrations of peppermint oil were introduced into the upper gastrointestinal tract of 40 patients undergoing the procedure. Duodenal relaxation was obtained with 20 mL of 1.6% peppermint oil solution and the procedure was performed successfully in 91.4% of patients. The inhibitory effect of peppermint oil appeared to be identical to that of glucagon, but without side effects (Yamamoto et al., 2006).

11.11 NAUSEA

A small study examined a variety of aromatherapy treatments to 25 patients suffering from nausea in a hospice and palliative care facility. Patients were offered the essential oils of *Foeniculum vulgare* var. *dulce*, *Chaemomelum nobile*, and *Mentha × piperita*, either singly or in blends, depending on individual preferences. Delivery methods included abdominal compress or massage, personal air spritzer or scentball diffuser. Only 32% of patients reported no response to the treatments and they had all just finished heavy courses of chemotherapy. Using a visual-numeric analogue scale, the remainder of patients experienced an improvement in their nausea symptoms when using the aromatherapy interventions. All patients were also taking antiemetic drugs and so the essential oils were regarded as successful complements to standard medications (Gilligan, 2005).

A 6-month trial investigated the effect of inhaled 5% *Zingiber officinale* essential oil in the prevention of postoperative nausea and vomiting (PONV). All patients were at a high risk for PONV and all used similar combinations of prophylactic intravenous antiemetics. The test group had the essential oil applied to the volar aspects of both wrists via a rollerball immediately prior to surgery. In the recovery room, patients were questioned as to their feelings of nausea. Any patient who felt that they required further medication was considered a “failure.” Prevention of PONV by ginger essential oil was effective in 80% of cases, as measured by no complaint of nausea during the recovery period. In those patients who did not receive the essential oil, 50% experienced nausea (Geiger, 2005).

Another experiment used essential oils to prevent PONV, but they were applied after surgery if the patient complained of nausea. An undiluted mixture of *Zingiber officinale*, *Elettaria cardamomum*, and *Artemisia dracunculus* essential oils in equal parts was applied with light friction to the sternocleidomastoid area and carotid-jugular axis of the neck. Of the 73 cases treated, 50 had a positive response, that is, a complete block of nausea and vomiting within 30 min. It was found that the best response (75%) was with patients who had received a single analgesic/anesthetic (de Pradier, 2006).

The use of essential oils to alleviate motion sickness has also been investigated. A blend of *Zingiber officinale*, *Lavandula angustifolia*, *Mentha spicata*, and *Mentha × piperita* essential oils in an inhalation dispenser (QueaseEase™) was given to 55 ocean boat passengers with a history of motion sickness. The oil blend was inhaled as needed during the trip and queasiness was assessed using a linear analogue scale. The product was more effective than the placebo in lowering sensations of nausea when the seas were roughest, but was not significant at other times (Post-White and Nichols, 2007).

11.12 PAIN RELIEF

There follows a number of differing conditions that have been treated with essential oils with varying biological activities, such as antispasmodic, anti-inflammatory, and so on. They all share a common effect, that of pain relief.
11.12.1 DYSMENORRHEA

The seeds of *Foeniculum vulgare* have been used in traditional remedies for the treatment of dysmenorrhea, an action attributed to the antispasmodic effect of the essential oil. An *in vitro* experiment demonstrated that fennel essential oil inhibited oxytocin- and prostaglandin E₂ (PGE₂)-induced contractions of isolated uterus; the former was considered to have a similar activity to diclofenac, a nonsteroidal anti-inflammatory drug. The overall mechanism of action is still unknown (Ostad et al., 2001).

A randomized, double-blind crossover study examined the effect of oral fennel essential oil at 1% or 2% concentration as compared to placebo for the treatment of 60 women with mild to moderate dysmenorrhea. Up to 1 mL of the solution was taken as required for the pain at intervals of not less than 4 h. In the treatment groups, the severity of the pain was significantly decreased; the efficacy of the 2% fennel oil was 67.4%, which was comparable to the efficacy of nonsteroidal anti-inflammatory drugs (Khorshidi et al., 2003).

Thirty patients with moderate to severe dysmenorrhea took part in a study to compare the activity of mefenamic acid with the essential oil of *Foeniculum vulgare* var. *dulce*. The evaluation was carried out during the first 5 days of three consecutive menstrual cycles. In the first cycle, no intervention was given (control); during the second cycle, 250 mg of mefenamic acid 6 hourly was prescribed; and in the third, 25 drops of a 2% solution of fennel essential oil were given 4 hourly. A self-scoring linear analogue technique was used to determine effect and potency. Both interventions effectively relieved menstrual pain as compared to the control. Mefenamic acid was more potent on the second and third days, but the result was not statistically significant. It was concluded that fennel essential oil was a safe and effective remedy but was probably less effective than mefenamic acid at the dosage used (Jahromi et al., 2003).

A third study used aromatherapy massage for the relief of the symptoms of dysmenorrhea in 67 students. The essential oils of *Lavandula officinalis*, *Salvia sclarea*, and *Rosa centifolia* (2:1:1 ratio) were diluted to 3% in 5 mL of almond oil and applied in a 15-min abdominal massage daily, 1 week before the start of menstruation, and stopping on the first day of menstruation. The control group received no treatment and the placebo group received massage with almond oil only. The results showed a significant improvement of dysmenorrhea as assessed by a verbal multidimensional scoring system for the essential oil group compared to the other two groups (Han et al., 2006).

11.12.2 Headache

The effect of peppermint and eucalyptus essential oils on the neurophysiological, psychological, and experimental algesimetric parameters of headache mechanisms were investigated using a double-blind, placebo-controlled trial with 32 healthy subjects. Measurements included sensitivity to mechanical, thermal, and ischemically induced pain. Four preparations consisting of varying amounts of peppermint and/or eucalyptus oils in ethanol were applied to the forehead and temples. Eucalyptus alone had no effect on the parameters studied. A combination of both oils (10% peppermint and 5% eucalyptus) increased cognitive performance and had a muscle-relaxing and mentally relaxing effect, but did not influence pain sensitivity. Peppermint alone (10%) had a significant analgesic effect with reduction in sensitivity to headache. It was shown to exert significant effects on the pathophysiological mechanisms of clinical headache syndromes (Göbel et al., 1995a).

A second study used the same essential oils when investigating the skin perfusion of the head in healthy subjects and migraine patients. In the former, capillary flow was increased by 225% in comparison with baseline by peppermint oil, while eucalyptus decreased the flow by 16%. In migraine patients, neither essential oil had any effect. It was suggested that the absence of capillary vasodilation (normally caused by menthol) was due to impaired calcium channel function in migraine patients (Göbel et al., 1995b).
11.12.3 INFANTILE COLIC

Since animal studies had demonstrated that the essential oil of *Foeniculum vulgare* reduced intestinal spasm and increased the motility of the small intestine, it was used in a double-blind, randomized, placebo-controlled trial in the treatment of infantile colic. The 125 infants were all 2–12 weeks of age and those in the treatment group received a water emulsion of 0.1% fennel essential oil and 0.4% polysorbate (5–20 mL) up to four times a day. The dose was estimated to provide about 12 mg/kg/day of fennel essential oil. The control group received the polysorbate only. The treatment provided a significant improvement of colic, eliminating symptoms in 65% of infants as compared to 23.7% for the control. No side effects were noted (Alexandrovich et al., 2003).

11.12.4 JOINT PHYSIOTHERAPY

Six sports physiotherapists treated 30 patients suffering from knee or ankle pathologies of traumatic or surgical origin. Two commercial products were used simultaneously, Dermasport® and Solution Cryo®. The former was a gel consisting of the essential oils of *Betula alba*, *Melaleuca leucadendron*, *Cinnamomum camphora*, *Syzygium aromaticum*, *Eucalyptus globulus*, and *Gaultheria procumbens*. Solution Cryo contained the same essential oils minus *Gaultheria procumbens* but with the addition of *Chamaemelum nobile*, *Citrus limon*, and *Cupressus sempervirens*. Both products were at an overall concentration of 6%. Thirty minutes after application a net reduction in movement pain and joint circumference was demonstrated, along with an increase in articular flexion and extension of both joints in all patients (Le Faou et al., 2005).

11.12.5 NIPPLE PAIN

Nipple cracks and pain are a common cause of breastfeeding cessation. In a randomized trial 196 primiparous women were studied during the first 2 weeks postpartum. The test group applied peppermint water (essential oil in water, concentration not given) to the nipple and areola after each breastfeed while the control group applied expressed breast milk. The overall nipple crack rate at the end of the period in the peppermint group was 7% as compared to 23% for the control. Only 2% of peppermint group experienced severe nipple pain in contrast to 23% of the control, with 93% and 71% experiencing no pain, respectively (Melli et al., 2007).

11.12.6 OSTEOARTHRITIS

A blend of *Zingiber officinale* (1%) and *Citrus sinensis* (0.5%) essential oils was used in an experimental double-blind study using 59 patients with moderate to severe knee pain caused by osteoarthritis. The treatment group received six massage sessions over a 3-week period; the placebo received the same massage sessions but without the essential oils and the control had no intervention. Assessment of pain intensity, stiffness, and physical functioning was carried out at baseline and at post 1 and 4 weeks. There were improvements in pain and function for the intervention group in comparison with the placebo and control at post 1 week but this was not sustained to week 4. The treatment was suggested for the relief of short-term knee pain (Yip et al., 2008).

11.12.7 POSTHERPETIC NEURALGIA

A double-blind crossover study examined the effect of the essential oil of *Pelargonium* spp. on moderate to severe postherpetic pain in 30 subjects. They were assigned to groups receiving 100, 50, or 10% geranium essential oil (in mineral oil), mineral oil placebo, or capsaicin control. Pain relief was measured using a visual analogue scale from 0 to 60 min after treatment. Mean values for the time integral of spontaneous pain reduction was 21.3, 12.7, and 8.0 for the 100%, 50%, and 10% geranium
oils and evoked pain-reduction values were 15.8, 7.7, and 5.9, respectively. Both evoked and spontaneous pains were thus significantly reduced in a dose-dependent manner (Greenway et al., 2003).

The result is interesting because topical capsaicin cream (one of the standard treatments for this condition) relieves pain gradually over 2 weeks, while the essential oil acted within minutes. Geranium essential oil applied cutaneously in animal studies has suppressed cellular inflammation and neutrophil accumulation in inflammatory sites (Maruyama et al., 2006) but postherpetic neuralgia normally occurs after the inflammation has subsided. One of the main components of the essential oil, geraniol, and the minor components of geranial, nerol, and neral, have been shown to interact with the transient receptor potential channel, TRPV1, as does capsaicin (Stotz et al., 2008). This sensory inhibition may explain the efficacy of topical geranium oil.

11.12.8 POSTOPERATIVE PAIN

A randomized, placebo-controlled clinical trial was conducted to determine whether the inhalation of lavender essential oil could reduce opioid requirements after laparoscopic adjustable gastric banding. In the postanesthesia care unit, 54 patients were given either lavender (two drops of a 2% dilution) or nonscented oil in a face mask. It was found that patients in the lavender group required significantly less morphine postoperatively than the placebo group (2.38 and 4.26 mg, respectively). Moreover, significantly more patients in the placebo group required analgesics in comparison with the lavender group; 82% compared to 46% (Kim et al., 2007).

A similar study in the previous year with 50 patients who had undergone breast biopsy surgery had found that lavender essential oil had no significant effect on postoperative pain or analgesic requirements. However, a significantly higher satisfaction with pain control was noted by patients in the lavender group (Kim et al., 2006).

11.12.9 PROSTATITIS

One study has evaluated the use of Rowatinex for the treatment of chronic prostatitis/chronic pelvic pain syndrome, the rationale being based on the known anti-inflammatory properties of the product. A 6-week, randomized single-blind trial compared the use of Rowatinex 200 mg thrice daily with ibuprofen 600 mg thrice daily in 50 patients. Efficacy was measured by the National Institutes of Health (NIH)-Chronic Prostatitis Symptom Index (NIH-CPSI) that was completed by the patients on four occasions. The decrease in the NIH-CPSI was significant in both groups at the end of treatment and a 25% improvement in the total score was superior in the Rowatinex group (68%) compared to the ibuprofen group (40%). Although the symptomatic response was significant, no patients became asymptomatic (Lee et al., 2006).

11.12.10 PRURITIS

Pruritis is one of the most common complications of patients undergoing hemodialysis. Thirteen such patients were given an arm massage with lavender and tea tree essential oils (5% dilution in sweet almond and jojoba oil) thrice a week for 4 weeks. A control group received no intervention. Pruritis score, pruritis-related biochemical markers, skin pH, and skin hydration were measured before and after the study. There was a significant decrease in the pruritis score and blood urea nitrogen level for the test group. The control group showed a decreased skin hydration between pre- and post-test whereas for the essential oil group it was significantly increased (Ro et al., 2002). The lack of a massage only group in the study meant that the effects could not be definitely associated with the essential oils.

11.13 PEDICULICIDAL ACTIVITY

The activity of essential oils against the human head louse, Pediculus humanus capitis, has been investigated in a number of reports. Numerous essential oils have been found to exhibit
pediculicidal activity in vitro, with common oils such as *Eucalyptus globulus*, *Origanum marjorana*, *Rosmarinus officinalis*, and *Elettaria cardamomum* being comparable to, or more effective than *d*-phenothrin and pyrethrum (Yang et al., 2004). *Melaleuca alternifolia* and *Lavandula angustifolia* have also been found to be highly effective pediculicidal agents (Williamson et al., 2007).

Despite the availability of positive in vitro results, only one trial involving application to humans has been documented; a mixture of anise and ylang ylang essential oils in coconut extract (Paranix®) was applied once to five children. Viable lice were not found after 7 days (Scanni and Bonifazi, 2006).

### 11.14 Recurrent Aphtous Stomatitis

Recurrent aphtous stomatitis (RAS), also known as canker sores, are the most common oral mucosal lesions and although the process is sometimes self-limiting, the ulcer activity is mostly continuous and some forms may last for 20 years. Predisposing agents include bacteria and fungi, stress, mouth trauma, certain medications, and food allergies. Two essential oils both endemic to Iran have been investigated for treatment of this condition: *Zataria multiflora*, a thyme-like plant containing thymol, carvacrol, and linalool as major components, and *Satureja khuzistanica* containing predominantly carvacrol.

In a double-blind, randomized study, 60 patients with RAS received either 30 mL of an oral mouthwash composed of 60 mg of *Zataria multiflora* essential oil in an aqueous-alcoholic solution or placebo thrice daily for 4 weeks. In the treatment group, 83% of patients responded well while 17% reported a deterioration of their condition. This was compared with 13% and 87% for the placebo group, respectively. A significant clinical improvement with regard to less pain and shorter duration of the condition was found in the essential oil group (Mansoori et al., 2002).

*Satureja khuzistanica* essential oil 0.2% v/v was prepared in a hydroalcoholic solution and used in double-blind, randomized trial with 60 RAS patients. Its activity was compared with a 25% hydroalcoholic extract of the same plant and a hydroalcoholic placebo. A cotton pad was impregnated with 5 drops of preparation and placed on the ulcers for 1 min (fasting for 30 min afterwards) four times a day. The results of the extract and the essential oil groups were similar, with a significantly lower time for both pain elimination and complete healing of the ulcers in comparison with the placebo (Amanlou et al., 2007). The reported antibacterial, analgesic, antioxidant, and anti-inflammatory activities of this essential oil (Abdollahi et al., 2003; Amanlou et al., 2004, 2005) were thought responsible for the result.

### 11.15 Respiratory Tract

Given the volatile nature of essential oils, it should come as no surprise that their ability to directly reach the site of intended activity via inhalation therapy has led to their use in the treatment of a range of respiratory conditions. Moreover, a number of components are effective when taken internally, since they are bioactive at the level of bronchial secretions during their excretion. With the exception of one report, all of the research has used the individual components of either 1,8-cineole or menthol, or has employed them in combination with several other isolated essential oil components within commercial preparations.

#### 11.15.1 Menthol

Menthol-containing essential oils have been used in the therapy of respiratory conditions for many years and the individual component is present in a wide range of over-the-counter medications. Of the eight optical isomers of menthol, *l*-(-)-menthol is the most abundant in nature and imparts a cooling sensation to the skin and mucous membranes.
Menthol is known to react with a temperature-sensitive (8–28°C range) transient receptor potential channel, leading to an increase in intracellular calcium, depolarization and initiation of an action potential (Jordt et al., 2003). This channel, known as TRPM8, is expressed in distinct populations of afferent neurons; primarily thinly myelinated Aδ cool fibers and to a lesser extent, unmyelinated C-fiber nociceptors (Thut et al., 2003). It is the interaction with the TRPM8 thermoreceptor that is responsible for the cooling effect of menthol when it is applied to the skin. This activity is not confined to the dermis, since the presence of TRPM8 has been demonstrated by animal experimentation in the squamous epithelium of the nasal vestibule (Clarke et al., 1992), the larynx (Sant’Ambrogio et al., 1991), and lung tissue (Wright et al., 1998). Thus the activation of cold receptors via inhaled menthol leads to a number of beneficial effects.

11.15.1.1 Antitussive
Despite being used as a component in cough remedies since the introduction of a “vaporub” in 1890, there are few human trials of menthol used alone as being effective. In a citric acid-induced cough model in healthy subjects, Packman and London (1980) found that menthol was effective, although 1,8-cineole was more efficacious. The use of an aromatic unction rather than direct inhalation may have affected the results, since the inhalation of menthol has been shown in animal models to be significantly more effective at cough frequency reduction (28% and 56% at 10 and 30 g/l, respectively) compared to 1,8-cineole (Laude et al., 1994).

A single-blind pseudorandomized crossover trial in 42 healthy children was used to compare the effect of an inhalation of either menthol or placebo on citric acid-induced cough. It was found that cough frequency was reduced in comparison with the baseline but not to that of the placebo (Kenia et al., 2008). However, the placebo chosen was eucalyptus oil, whose main component is 1,8-cineole and known to have similar antitussive properties to menthol.

Along with other ion channel modulators, menthol is recognized as a potential “novel therapy” for the treatment of chronic cough (Morice et al., 2004, p. 489). It is not clear whether the antitussive activity of menthol is due solely to its stimulation of airway cold receptors; it may also involve pulmonary C-fibers (a percentage of which also express TRPM8) or there may be a specific interaction with the neuronal cough reflex.

11.15.1.2 Nasal Decongestant
Menthol is often thought of as a decongestant, but this effect is a sensory illusion. Burrow et al. (1983) and Eccles et al. (1988) showed that there was no change in nasal resistance to airflow during inhalation of menthol, although the sensation of nasal airflow was enhanced. In the former experiment, 1,8-cineole and camphor were also shown to enhance the sensation of airflow, but to a lesser extent than menthol.

In a double-blind, randomized trial subjects suffering from the common cold were given lozenges containing 11 mg of menthol. Posterior rhinomanometry could detect no change in nasal resistance to airflow after 10 min; however, there were significant changes in the nasal sensation of airflow (Eccles et al., 1990).

A single-blind pseudorandomized crossover trial compared the effect of an inhalation of either menthol or placebo. The main outcome measures were nasal expiratory and inspiratory flows and volumes, as measured by a spirometer and the perception of nasal patency, assessed with a visual analogue scale. It was found that there was no effect of menthol on any of the spirometric measurements although there was a significant increase in the perception of nasal patency (Kenia et al., 2008).

Thus it has been demonstrated that menthol is not a nasal decongestant. However, it is useful in therapy since stimulation of the cold receptors causes a subjective sensation of nasal decongestion and so relieves the feeling of a blocked nose. In commercial preparations that include menthol, a true decongestant such as oxymetazoline hydrochloride is often present.
11.15.1.3 Inhibition of Respiratory Drive and Respiratory Comfort

When cold air was circulated through the nose in human breath-hold experiments, subjects were able to hold their breath longer (McBride and Whitelaw, 1981) and inhaling cold air was shown to inhibit normal breathing patterns (Burgess and Whitelaw, 1988). This indicated that cold receptors could be one source of monitoring inspiratory flow rate and volume. Several animal experiments demonstrated that the inhalation of cold air, warm air, plus menthol, or menthol alone (390 ng/mL) significantly enhanced ventilator inhibition (Orani et al., 1991; Sant'Ambrogio et al., 1992).

Sloan et al. (1993) conducted breath-hold experiments with 20 healthy volunteers. The ingestion of a lozenge containing 11 mg of menthol significantly increased the hold time, indicating a depression of the ventilatory drive. It was later postulated by Eccles (2000) that in addition to chemoreceptors detecting oxygen and carbon dioxide in the blood, cold receptors in the respiratory tract may also modulate the drive to breathe.

Eleven healthy subjects breathed through a device that had either an elastic load or a flow-resistant load. Sensations of respiratory discomfort were compared using a visual analogue scale before, during, and after inhalation of menthol. It was found that the discomfort associated with loaded breathing was significantly reduced and was more effective during flow-resistive loading than elastic loading. Inhalation of another fragrance had no effect and so the result was attributed to a direct stimulation of cold receptors by menthol, a reduction in respiratory drive being perhaps responsible (Nishino et al., 1997).

During an investigation of dyspnea, the effect of menthol inhalation on respiratory discomfort during loaded breathing was found to be inconsistent. Further tests found that the effect of menthol was most important during the first few minutes of inhalation and in the presence of high loads (Peiffer et al., 2001). The therapeutic application of menthol in the alleviation of dyspnea has yet to be described.

11.15.1.4 Bronchodilation and Airway Hyperresponsiveness

The spasmolytic activity of menthol on airway smooth muscle has been demonstrated in vitro (Taddei et al., 1988). To examine the bronchodilatory effects of menthol, a small trial was conducted on six patients with mild to moderate asthma. A poultice-containing menthol was applied daily for 4 weeks and it was found that bronchoconstriction was decreased and airway hyperresponsiveness improved (Chiyotani et al., 1994b).

A randomized, placebo-controlled trial examined the effects of menthol (10 mg nebulized twice daily for 4 weeks) on airway hyperresponsiveness in 23 patients with mild to moderate asthma. The diurnal variation in the peak expiratory flow rate (a value reflecting airway hyperexcitability) was decreased but the forced expiratory volume was not significantly altered. This indicated an improvement of airway hyperresponsiveness without affecting airflow limitation (Tamaoki et al., 1995). Later in vivo research examined the effect of menthol on airway resistance caused by capsaicin- and neurokinin-induced bronchoconstriction; there was a significant decrease in both cases by inhalation of menthol at 7.5 μg/L air concentration. The in vitro effect of menthol on bronchial rings was also studied. It was concluded that menthol attenuated bronchoconstriction by a direct action on bronchial smooth muscle (Wright et al., 1997).

In cases of asthma, the beneficial effects of menthol seem to be mainly due to its bronchodilatory activity on smooth muscle; interaction with cold receptors and the respiratory drive may also play an important role.

Recent in vitro studies have shown that a subpopulation of airway vagal afferent nerves expresses TRPM8 receptors and that activation of these receptors by cold and menthol excite these airway autonomic nerves. Thus, activation of TRPM8 receptors may provoke an autonomic nerve reflex to increase airway resistance. It was postulated that this autonomic response could provoke menthol- or cold-induced exacerbation of asthma and other pulmonary disorders (Xing et al., 2008).
cold stimulation or inhalation of menthol can cause immediate airway constriction and asthma in some people; perhaps the TRPM8 receptor expression is upregulated in these subjects. The situation is far from clear.

11.15.1.5 Summary
The respiratory effects of menthol that have been demonstrated are as follows:

1. Antitussive at low concentration.
2. Increases the sensation of nasal airflow giving the impression of decongestion.
3. No physical decongestant activity.
4. Depresses ventilation and the respiratory drive at comparatively higher concentration.
5. Reduces respiratory discomfort and sensations of dyspnea.

A number of *in vitro* and animal experiments have demonstrated the bronchomucotropic activity of menthol (Boyd and Sheppard, 1969; Welsh et al., 1980; Chiyotani et al., 1994a), whereas there have been conflicting reports as to whether menthol is a mucociliatory stimulant (Das et al., 1970) or is ciliotoxic (Su et al., 1993). Apart from the inclusion of relatively small quantities of menthol in commercial preparations that have known beneficial mucociliary effects, there are no documented human trials to support the presence of these activities.

11.15.2 1,8-Cineole
This oxide has a number of biological activities that make it particularly useful in the treatment of the respiratory tract. 1,8-Cineole has been registered as a licensed medication in Germany for over 20 years and is available as enteric-coated capsules (Soledum®). It is therefore not surprising that the majority of the trials originate from this country and use oral dosing of 1,8-cineole instead of inhalation. Rather than discuss specific pathologies, the individual activities will be examined and their relevance (alone or in combination) in treatment regimes should become apparent.

11.15.2.1 Antimicrobial
The anti-infectious properties of essential oils high in 1,8-cineole content may warrant their inclusion into a treatment regime but other components are more effective in this regard. 1,8-Cineole is often considered to have marginal or no antibacterial activity (Kotan et al., 2007), although it is very effective at causing leakage of bacterial cell membranes (Carson et al., 2002). It may thus allow more active components to enter the bacteria by permeabilizing their membranes.

1,8-Cineole does possess noted antiviral properties compared to the common essential oil components of borneol, citral, geraniol, limonene, linalool, menthol, and thymol; only that of eugenol was greater (Bourne et al., 1999). However, in comparison with the potent thujone, the antiviral potential of 1,8-cineole was considered relatively low (Sivropoulou et al., 1997).

A placebo-controlled, double-blind, randomized parallel-group trial examined the long-term treatment of 246 chronic bronchitics during winter with myrtol standardized Gelomyrtof® forte. This established German preparation consists mainly of 15% α-pinene, 35% limonene, and 47% 1,8-cineole and was administered thrice daily in 300 mg capsules. It was found to reduce the requirement for antibiotics during acute exacerbations; 51.6% compared to 61.2% under placebo. Of those patients needing antibiotics, 62.5% in the test group required them for ≤7 days whereas 76.7% of patients in the placebo group needed antibiotics for more than 7 days. Moreover, 72% of patients remained without acute exacerbations in the test group compared to 53% in the placebo group (Meister et al., 1999).

Although emphasis was given to antibiotic reduction, a significant antimicrobial effect by the preparation is unlikely to have paid an important contribution. Indeed, Meister et al. refer to reduced health impairment due to sputum expectoration and cough, and note other beneficial properties of 1,8-cineole that will be discussed in Sections 11.15.2.2 through 11.15.2.6.
11.15.2.2 Antitussive

The antitussive effects of 1,8-cineole were first proven by Packman and London in 1980, who induced coughing in 32 healthy human subjects via the use of an aerosol spray containing citric acid. This single-blind crossover study examined the effect of a commercially available chest rub containing, among others, eucalyptus essential oil. The rub was applied to the chest in a 7.5 mg dose and massaged for 10–15 s after which the frequency of the induced coughing was noted. It was found that the chest rub produced a significant decrease in the induced cough counts and that eucalyptus oil was the most active component of the rub.

1,8-Cineole interacts with TRPM8, the cool-sensitive thermoreceptor that is primarily affected by menthol. In comparison with menthol, the effect of 1,8-cineole on TRPM8 (as measured by Ca2+ influx kinetics) is much slower and declines more rapidly (Behrendt et al., 2004). In a similar manner to menthol, the antitussive activity of 1,8-cineole may be due in part to its stimulation of airway cold receptors.

11.15.2.3 Bronchodilation

In vitro tests using guinea pig trachea determined that the essential oil of *Eucalyptus tereticornis* had a myorelaxant, dose-dependent effect (10–1000 μg/mL) on airway smooth muscle, reducing tracheal basal tone and K+–induced contractions, as well as attenuating acetylcholine-induced contractions at higher concentrations (Coelho-de-Souza et al., 2005). This activity was found to be mainly due to 1,8-cineole, although the overall effect was thought due to a synergistic relationship between the oxide and α- and β-pinene. Similar results were obtained using the essential oil of *Croton nepetaefolius*, whose major component was also 1,8-cineole (Magalhães et al., 2003).

A double-blind, randomized clinical trial over 7 days compared oral pure 1,8-cineole (3 ¥ 200 mg/day) to Ambroxol (3 ¥ 30 mg/day) in 29 patients with chronic obstructive pulmonary disease (COPD). Vital capacity, airway resistance, and specific airway conductance improved significantly for both drugs, whereas the intrathoracic gas volume was reduced by 1,8-cineole but not by Ambroxol. All parameters of lung function, peak flow, and symptoms of dyspnea were improved by 1,8-cineole therapy, but were not statistically significant in comparison with Ambroxol due to the small number of patients. In addition to other properties, it was noted that the oxide seemed to have bronchodilatory effects (Wittman et al., 1998).

11.15.2.4 Mucolytic and Mucociliary Effects

Mucolytics break down or dissolve mucus and thus facilitate the easier removal of these secretions from the respiratory tract by the ciliated epithelium, a process known as mucociliary clearance. Some mucolytics also have a direct action on the mucociliary apparatus itself.

Administered via steam inhalation to rabbits, 1,8-cineole in concentrations that produced a barely detectable scent (1–9 mg/kg) augmented the volume output of respiratory tract fluid from 9.5% to 45.3% (Boyd and Sheppard, 1971), an effect that they described as “mucotropic.” Interestingly, in the same experiment fenchone at 9 mg/kg increased the output by 186.2%, thus confirming the strong effects of some ketones in this regard. Also using rabbits, Zanker (1983) found that oxygenated monoterprenoids reduced mucus deposition and partially recovered the activity of ciliated epithelium.

Because of these early animal experiments, the beneficial effects of 1,8-cineole on mucociliary clearance have been clearly demonstrated in a number of human trials. Dorow et al. (1987) examined the effects of a 7-day course of either Gelomyrtol forte (4 ¥ 300 mg/day) or Ambroxol (3 ¥ 30 mg/day) in 20 patients with chronic obstructive bronchitis. Improved mucociliary clearance was observed in both groups, although improvement in lung function was not detected.

Twelve patients with chronic obstructive bronchitis were given a 4-day treatment with 1,8-cineole (4 ¥ 200 mg/day). By measuring the reduction in percentage radioactivity of an applied radioaerosol, significant improvements in mucociliary clearance were demonstrated at the 60 and 120 min after each administration (Dorow, 1989).

In a small double-blind study, the expectorant effect of Gelomyrtol forte (1 ¥ 300 mg/day, 14 days) was examined in 20 patients with chronic obstructive bronchitis. The ability to expectorate,
frequency of coughing attacks, and shortness of breath were all improved by the therapy, as was sputum volume and color. Both patients and physicians rated the effects of Gelomyrtol forte as better than the placebo, but due to the small group size statistically significant differences could not be demonstrated (Ulmer and Schött, 1991).

A randomized, double-blind, placebo-controlled trial was used to investigate the use of mucolytics to alleviate acute bronchitis (Mattys et al., 2000). They compared Gelomyrtol forte (4 × 300 mg, days 1–14), with Ambroxol (3 × 30 mg, days 1–3; 2 × 30 mg, days 4–14) and Cefuroxime (2 × 250 mg, days 1–6) in 676 patients. By monitoring cough frequency data, regression of the frequency of abnormal auscultation, hoarseness, headache, joint pain, and fatigue, it was shown that Gelomyrtol forte was very efficacious and comparable to the other active treatments. Overall, it scored slightly more than Ambroxol and Cefuroxime and was therefore considered to be a well-evidenced alternative to antibiotics for acute bronchitis.

Several studies have demonstrated a direct effect of 1,8-cineole on the ciliated epithelium itself. Kaspar et al. (1994) conducted a randomized, double-blind three-way crossover 4-day study of the effects of 1,8-cineole (3 × 200 mg/day) or Ambroxol (3 × 30 mg/day) on mucociliary clearance in 30 patients with COPD. Treatment with the oxide resulted in a statistically significant increase in the ciliary beat frequency of nasal cilia, a phenomenon that did not occur with the use of Ambroxol (an increase of 8.2% and 1.1%, respectively). A decrease of “saccharine-time” was clinically relevant and significant after 1,8-cineole therapy (241 s) but not after Ambroxol (48 s). Lung function parameters were significantly improved equally by both drugs.

After the ingestion of Gelomyrtol forte (3 × 1 capsule/day for 4 days) by four healthy persons and one person after sinus surgery, there was a strong increase in mucociliary transport velocity, as detected by movement of a radiolabeled component (Behrbohm et al., 1995).

In sinusitis, the ciliated beat frequency is reduced and 30% of ciliated cells convert to mucus-secreting goblet cells. The impaired mucociliary transport, excessive secretion of mucus, and edema block drainage sites leading to congestion, pain, and pressure.

To demonstrate the importance of drainage and ventilation of sinuses as a therapeutic concept, Federspil et al. (1997) conducted a double-blind, randomized, placebo-controlled trial using 331 patients with acute sinusitis. The secretolytic effects of Gelomyrtol forte (300 mg) over a 6-day period proved to be significantly better than the placebo.

Kehrl et al. (2004) used the known stimulatory effects of 1,8-cineole on ciliated epithelium and its mucolytic effect as a rationale for treating 152 acute rhinosinusitis patients in a randomized, double-blind, placebo-controlled study. The treatment group received 3 × 200 mg 1,8-cineole daily for 7 days. There was a clinically relevant and significant improvement in frontal headache, headache on bending, pressure point sensitivity of the trigeminal nerve, nasal obstruction, and rhinological secretions in the test group, as compared to the control group. It was concluded that 1,8-cineole was a safe and effective treatment for acute nonpurulent rhinosinusitis before antibiotics are indicated.

11.15.2.5 Anti-Inflammatory Activity
The effects of 1,8-cineole on stimulated human monocyte mediator production were studied in vitro and compared with that of budesonide, a corticosteroid agent with anti-inflammatory and immunosuppressive effects (Juergens et al., 1998a). At therapeutic levels, both substances demonstrated a similar inhibition of the inflammatory mediators leukotriene B₄ (LTB₄), PGE₂, and interleukin-1β (IL-1β). This was the first evidence of a steroid-like inhibition of arachidonic acid metabolism and IL-1β production by 1,8-cineole.

Later that year, the same team (Juergens et al., 1998b) reported a dose-dependent and highly significant inhibition of tumor necrosis factor-α (TNF-α), IL-1β, thromboxane B₂, and LTB₄ production by 1,8-cineole from stimulated human monocytes in vitro.

A third experiment combined ex vivo and in vivo testing; 10 patients with bronchial asthma were given 3 × 200 mg of 1,8-cineole daily for 3 days. Lung function was measured before the first dose, at the end of the third dose and 4 days after discontinuation of the therapy. At the same time, blood
samples were taken from which monocytes were collected and stimulated ex vivo for LTB$_4$ and PGE$_2$ production. Twelve healthy volunteers also underwent the treatment and their blood was taken for testing. It was found that by the end of the treatment and 4 days after, the production of LTB$_4$ and PGE$_2$ from the monocytes of both asthmatics and healthy individuals was significantly inhibited. Lung function parameters of asthmatic patients were significantly improved (Juergens et al., 1998c).

These three reports suggested a strong anti-inflammatory activity of 1,8-cineole via both the cyclooxygenase and 5-lipoxygenase pathways, and the possibility of a new, well-tolerated treatment of airway inflammation in obstructive airway disease.

Juergens et al. (2003) conducted a double-blind, placebo-controlled clinical trial involving 32 patients with steroid-dependent severe bronchial asthma. The subjects were randomly assigned to receive either a placebo or a $3 \times 200$ mg 1,8-cineole daily for 12 weeks. Oral glucocorticosteroids were reduced by 2.5 mg increments every 3 weeks with the aim of establishing the glucocorticosteroid-sparing capacity of 1,8-cineole. The majority of asthma patients receiving oral 1,8-cineole remained clinically stable despite a mean reduction of oral prednisolone dosage of 36%, equivalent to 3.8 mg/day. In the placebo group, where only four patients could tolerate a steroid decrease, the mean reduction was 7%, equivalent to 0.9 mg/day. Compared with the placebo group, 1,8-cineole recipients maintained their lung function four times longer despite receiving lower doses of prednisolone.

Increased mucus secretion often appears as an initial symptom in exacerbated COPD and asthma, where stimulated mediator cells migrate to the lungs to produce cytokines; of particular importance are TNF-$\alpha$, IL-1$\beta$, IL-6, and IL-8 and those known to induce immunoglobulin E (IgE) antibody synthesis and maintain allergic eosinophilic inflammation (IL-4 and IL-5). Therefore, a study was conducted to investigate the role of 1,8-cineole in inhibiting cytokine production in stimulated human monocytes and lymphocytes in vitro (Juergens et al., 2004). It was shown that 1,8-cineole is a strong inhibitor of TNF-$\alpha$ and IL-1$\beta$ in both cell types. At known therapeutic blood levels, it also had an inhibitory effect on the production of the chemotactic cytokines IL-8 and IL-5 and may possess additional antiallergic activity by blocking IL-4 production.

A clinically relevant anti-inflammatory activity of 1,8-cineole has thus been proven for therapeutic use in airway diseases.

11.15.2.6 Pulmonary Function
An inhaler was used to apply 1,8-cineole (Soledum Balm) to 24 patients with asthma or chronic bronchitis in an 8-day-controlled trial. In all but one patient, an objective rise in expiratory peak flow values was demonstrated. The subjective experience of their illness was significantly improved for all subjects (Grimm, 1987).

In an open trial of 100 chronic bronchitics using both inhaled ($4 \times 200$ mg) and oral ($3 \times 200$ mg) 1,8-cineole over 7 days, the clinical parameters of forced vital capacity, forced expiratory volume, peak expiratory flow, and residual volume were all significantly improved when compared to initial values before treatment (Mahlo, 1990).

In a randomized, double-blind, placebo-controlled study of 51 patients with COPD, 1,8-cineole ($3 \times 200$ mg/day) was given for 8 weeks. For the objective lung functions of “airway resistance” and “specific airway resistance,” there was a clinically significant reduction of 21% and 26%, respectively. The improvement was attributed to a positive influence on disturbed breathing patterns, mucociliary clearance, and anti-inflammatory effects (Habich and Repges, 1994).

The majority of the in vivo trials involving 1,8-cineole report good, if not significant, changes in lung function parameters, whether the investigation concerns the common cold or COPD. This is not a convenient, accidental side effect of treatment but is a direct result of one or more of the factors already discussed that have direct effects on the pathophysiology of the airways. The ability to breathe more effectively and easily is an important consequence of the therapy that is sometimes minimized when dealing with the specific complexities of infection, inflammation, and so on. A compilation of human trials with 1,8-cineole is given in Table 11.3.
Table 11.3
Summary of Human Trials Demonstrating the Beneficial Effects of 1,8-Cineole in Various Respiratory Conditions

<table>
<thead>
<tr>
<th>Patients</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Cineole inhalation, 8 days</td>
<td>Objective rise in expiratory peak flow found. Subjective experiences of illness significantly improved</td>
<td>Grimm (1987)</td>
</tr>
<tr>
<td>10</td>
<td>Cineole 3 × 200 mg daily, 3 days</td>
<td>LTB₄ and PGE₂ production by monocytes was significantly inhibited. Lung functions were significantly improved</td>
<td>Juergens et al. (1998c)</td>
</tr>
<tr>
<td>32</td>
<td>Cineole 3 × 200 mg daily, 12 weeks</td>
<td>Twelve of 16 patients in cineole group remained stable despite a 36% reduction in oral steroid dosage</td>
<td>Juergens et al. (2003)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Acute bronchitis</strong></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>Vaporub 3 min</td>
<td>Decreased breathing frequency, suggesting “easier breathing”</td>
<td>Berger et al. (1978a)</td>
</tr>
<tr>
<td>676</td>
<td>Gelomyrtol 4 × 300 mg daily, 14 days</td>
<td>Coughing, sputum consistency, well-being, bronchial hyperreactivity, and associated symptoms all improved similarly by Gelomyrtol, Ambroxol, and Cefuroxime</td>
<td>Mattys et al. (2000)</td>
</tr>
<tr>
<td>9</td>
<td>Cineole inhalation, 8 days</td>
<td>Objective rise in expiratory peak flow found. Subjective experiences of illness significantly improved</td>
<td>Grimm (1987)</td>
</tr>
<tr>
<td>100</td>
<td>Cineole 3 × 200 mg daily, 7 days</td>
<td>All lung function parameters significantly improved</td>
<td>Mahlo (1990)</td>
</tr>
<tr>
<td>246</td>
<td>Gelomyrtol 3 × 300 mg daily, 6 months</td>
<td>Reduced acute exacerbations, reduced requirement for antibiotics, reduced treatment times when antibiotics taken. Well-being significantly improved</td>
<td>Meister et al. (1999)</td>
</tr>
<tr>
<td>20</td>
<td>Gelomyrtol 4 × 0.3 g daily, 7 days</td>
<td>Improved mucociliary clearance</td>
<td>Dorow et al. (1987)</td>
</tr>
<tr>
<td>20</td>
<td>Gelomyrtol 1 × 0.3 g daily, 14 days</td>
<td>All parameters relating to coughing improved. Sputum volume increased</td>
<td>Ulmer and Schött (1991)</td>
</tr>
<tr>
<td>12</td>
<td>Cineole 4 × 200 mg, 4 days</td>
<td>Significant improvement of mucociliary clearance</td>
<td>Dorow (1989)</td>
</tr>
<tr>
<td>51 including 16 asthmatics</td>
<td>Cineole 3 × 200 mg daily, 8 weeks</td>
<td>Significant improvement in airway resistance (21%), positive effects on sputum output and dyspnea</td>
<td>Habich and Repges (1994)</td>
</tr>
<tr>
<td>30</td>
<td>Cineole 1 × 200 mg daily, 4 days</td>
<td>Significant improvements in lung functions of FVC and FEV₁ (Ambroxol and cineole equieffective), significant increase in ciliary beat frequency</td>
<td>Kaspar et al. (1994)</td>
</tr>
<tr>
<td>29</td>
<td>Cineole 3 × 200 mg daily, 7 days</td>
<td>All lung function parameters, peak flow and dyspnea improved from day 1 onward</td>
<td>Wittmann et al. (1998)</td>
</tr>
<tr>
<td>24</td>
<td>Eucalyptus oil (9% of a mixture)</td>
<td>Reversed lung function abnormalities in small and large airways</td>
<td>Cohen and Dressler (1982)</td>
</tr>
<tr>
<td>331</td>
<td>Gelomyrtol 300 mg, 6 days</td>
<td>Effective treatment instead of antibiotics</td>
<td>Federspil et al. (1997)</td>
</tr>
<tr>
<td>152</td>
<td>Cineole 3 × 200 mg daily, 7 days</td>
<td>Effective reduction of symptoms without the need for antibiotics</td>
<td>Kehrl et al. (2004)</td>
</tr>
</tbody>
</table>
11.15.2.7 Summary
Although discussed separately, the multifaceted activities of 1,8-cineole perform together in harmony to provide an effective intervention that can inherently adapt to the needs of the individual patient. As already described, 1,8-cineole is known to possess the following properties:

1. Antimicrobial
2. Antitussive
3. Bronchodilatory
4. Mucolytic
5. Ciliary transport promotion
6. Anti-inflammatory
7. Lung function improvement.

Therefore, it may be seen that a diverse range of respiratory conditions of varying complexities will benefit from the use of pure 1,8-cineole or from essential oils containing this oxide as a major component.

11.15.3 Treatment with Blends Containing Both Menthol and 1,8-Cineole
A study measured transthoracic impedance pneumographs of 60 young children (2–40 months) with acute bronchitis before and after a 3-min application of Vaporub® to the back and chest. The data showed an early increase in amplitude up to 33%, which slowly descended during the 70-min post-treatment period to slightly above the control. Breathing frequency progressively decreased during the same period by 19.4%. Clinical observations combined with these results suggested a condition of “easier breathing” (Berger et al., 1978a). Currently, the active ingredients of Vaporub are camphor 4.8%, 1,8-cineole 1.2%, and menthol 2.6, but these components and percentages may have changed over the years.

The same team employed a similar experiment but used the pneumographic data to examine the quiet periods, that is, parts of the pneumogram where changes in the baseline were at least half of the average amplitude in more than five consecutive breathing excursions. It was found that the application of Vaporub increased quiet periods by up to 213.8%, whereas the controls (petroleum jelly application or rubbing only) never exceeded 62.4%. Thus the breathing restlessness of children with bronchitis was diminished and this was confirmed by clinical observations (Berger et al., 1978b).

By the measurement of lung and forced expiratory volumes, nasal, lower, and total airway resistances, closing volume data, the phase III slope of the alveolar plateau, and the maximum expiratory flow volume, peripheral airway dysfunction was confirmed in 24 adults with common colds. In a randomized, controlled trial, an aromatic mixture of menthol, eucalyptus oil, and camphor (56%, 9%, and 35% w/w, respectively) were vaporized in a room where the subjects were seated. Respiratory function measurements were made at baseline, 20 and 60 min after exposure. After the last measurement, phenylephrine was sprayed into the nostrils and the measurements taken again 5–10 min later to determine potential airway responsiveness. The control consisted of tap water. The results showed significant changes in forced vital capacity, forced expiratory volume, closing capacity, and the phase III slope after aromatic therapy as compared to the control. It was concluded that the aromatic inhalation favorably modified the peripheral airway dysfunction (Cohen and Dressler, 1982).

In a randomized, placebo-controlled trial of citric acid-induced cough in 20 healthy subjects, the inhalation of a combination of menthol and eucalyptus oil (75% and 25%, respectively) significantly decreased the cough frequency (Morice et al., 1994).

The effect of an aromatic inunction (Vaporub) was studied by the inhalation of a radioaerosol in a randomized, single-blinded, placebo-controlled crossover trial with 12 chronic bronchitics. It was found that after the application of 7.5 g of the product to the chest, removal of the tracheobronchial
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deposit was significantly enhanced at 30 and 60 min postinhalation, although further effects could not be demonstrated during the following 5 h, despite further application of the rub. During the first hour, mucociliary clearance was correlated with the concentration level of the aromatics (Hasani et al., 2003).

Another commercial preparation Pinimenthol®, a mixture of eucalyptus and pine needle oils plus menthol, reduced bronchospasm and demonstrated significant secretolytic effects when insufflated through the respiratory tract and when applied to the epilated skin of animals (Schäfer and Schäfer, 1981). In addition to the known effects of menthol and 1,8-cineole, pine needle oil is considered to be weakly antiseptic and secretolytic (Approved Herbs, 1998).

In a randomized, double-blind 14-day trial, 100 patients with chronic obstructive bronchitis received a combination of theophylline with β-adrenergica 2–3 times daily. The test group also received Pinimenthol. The parameters were investigated were objective (measurement of lung function and sputum) and subjective (cough, respiratory insufficiency, and pulmonary murmur). All differences in the subjective evaluations were statistically significant and of clinical importance; secretolysis was clearly shown. The addition of Pinimenthol showed a clear superiority to the basic combination therapy alone (Linsenmann and Swoboda, 1986).

A postmarketing survey was conducted of 3060 patients prescribed Pinimenthol suffering from cold, acute or chronic bronchitis, bronchial catarrh, or hoarseness. The product was given by inunction (29.6%), inhalation (17.3%), or inunction and inhalation (53.1%). Only 22 patients reported adverse effects and the efficacy of the product was judged as excellent or good by 88.3% of physicians and 88.1% of patients (Kamin and Kieser, 2007).

11.16 ALLERGIC RHINITIS

In a proof of concept study, a nasal spray was made from the essential oil of Artemisia abrotanum L. (4 mg/mL) and flavonoid extracts (2.5 μg/mL) from the same plant. The essential oil consisted primarily of 1,8-cineole and davanone at approximately 40% and 50%, respectively. Apart from a spasmolytic activity (Perfumi et al., 1995), little is known about the biological activity of davanone. The flavonoids present were thought to inhibit histamine release and interfere with arachidonic acid metabolism. The nasal spray was self-administered by 12 patients with allergic rhinitis, allergic conjunctivitis, and/or bronchial obstructive disease. They were instructed to use 1–2 puffs in each nostril at the first sign of symptoms, to a maximum of six treatments per day. All patients experienced rapid and significant relief of nasal symptoms and for those with allergic conjunctivitis, a significant relief of subjective eye symptoms was also experienced. Three of six patients with bronchial obstructive disease experienced rapid and clinically significant bronchial relief (Remberg et al., 2004).

11.17 SNORING

A blend of 15 essential oils was developed into a commercial product called “Helps stop snoring” and 140 adult snorers were recruited into a randomized trial using the product as a spray or gargle. Visual analogue scales were completed by the snorers’ partners relating to sleep disturbance each night. The treatment lasted for 14 days and results were compared to a prettrial period of the same length. The partners of 82% of the patients using the spray and 71% of patients using the gargle reported a reduction in snoring. This was compared to 44% of placebo users. The mode of action was postulated as being antispasmodic to the soft palate and pharynx (Pritchard, 2004).

11.18 SWALLOWING DYSFUNCTION

A delayed triggering of the swallowing reflex, mainly in elderly people, predisposes to aspiration pneumonia. To improve dysphagia, two different approaches using essential oils have been tried with success.
As black pepper is a strong appetite stimulant, it was postulated that nasal inhalation of the essential oil may stimulate cerebral blood flow in the insular cortex, the dysfunction of which has been reported to play a role in dysphagia. A randomized, controlled study of 105 elderly patients found that the inhalation of black pepper oil for 1 min significantly shortened the delayed swallowing time and increased the number of swallowing movements. Emission computed tomography demonstrated activation of the anterior cingulate cortex by the treatment. The inhalation of lavender essential oil or water had no effects (Ebihara et al., 2006a).

A second study used the established stimulating effects of menthol on cold receptors, since cold stimulation was known to restore sensitivity to trigger the swallowing reflex in dysphagic patients. Menthol was introduced into the pharynx of patients with mild to moderate dysphagia via a nasal catheter. The latent time of swallowing reflex was reduced significantly by menthol in a concentration-dependent manner; $10^{-2}$ menthol reduced the time to 9.4 s as compared to 13.8 s for distilled water. The use of a menthol lozenge before meals was thought appropriate (Ebihara et al., 2006b).

## 11.19 CONCLUSION

It is apparent from the diverse range of conditions that have benefitted from the administration of essential oils that their therapeutic potential is vast and yet underdeveloped. Moreover, since they are not composed of a single “magic bullet” with one target, they often have multiple effects that have additive or synergistic properties within a treatment regime.

A great many research papers investigating the bioactivity of essential oils conclude that the results are very encouraging and that clinical trials are the next step. For the majority, this step is never taken. The expense is one limiting factor and it is not surprising that clinical trials are mostly conducted once the essential oils have been formulated into a commercial product that has financial backing. It is evident that many of the claims made for essential oils in therapeutic applications have not been substantiated and an evidence base is clearly lacking. However, there is similarly a lack of research to demonstrate that essential oils are not effective interventions.

With the continuing search for new medicaments from natural sources, especially in the realm of antimicrobial therapy, it is hoped that future research into the efficacy of essential oils will be both stimulated and funded.

## REFERENCES


