Challenges Facing Essential Oil Therapy: Proof of Safety

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In any healing modality, evidence of both efficacy and safety are a reasonable expectation. Some of the challenges of current essential oil therapy practice include:

* What does "proof of safety" entail?
* Can essential oils be harmful as used in aromatherapy?
* Essential oil quality and integrity
* Is there in fact any benefit?
* How to balance risk and benefit?
* Misinformation & bias
* Flawed or unreasonable legislation

"Proof of safety"
Evidence that the real-world use of an essential oil presents either negligible or acceptable risk.

Because there is little clinical information for many essential oils, extrapolation from constituent data is often undertaken. However, this can result in misleading conclusions. Dose or concentration is a useful guide to safety, since greater amounts always increase risk, but an extremely low dose is pointless if it results in no effect. In addition to dose, at-risk groups such as young children, and individual health status may affect outcome.

Proof of <u>absolute</u> safety does not exist, because nothing is absolutely devoid of risk. Everything we eat, drink and breathe contains substances that, as single chemicals, are toxic. Contact with potentially harmful chemicals is a fact of modern life, though not necessarily hazardous.

Acetaldehyde, for example, an alcohol metabolite, is a carcinogen (Seitz & Stickel 2007), but it is also found in many fruits, vegetables and other foods; also very few essential oils. However, in the context of foods it is not regarded as dangerous, because of (a) the very small amount present, and (b) the co-presence of antioxidants and antimutagens. Our bodies have evolved to deal with small quantities of "toxins", which is why we have an immune system, antioxidant enzymes, base repair enzymes etc.

Essential oils may contain low concentrations of toxic constituents. They may even contain large amounts.

Can essential oils be harmful as used in aromatherapy?
Some of the major areas of concern include:

* Overdose
* Neurotoxins
* Inhaled allergens
* Adverse skin reactions
* Carcinogens

Overdose
Generally accidental, overdose has resulted in fatalities, most commonly in very young children who remove the cap from a bottle of essential oil and drink the contents. There have also been fatalities in adults, some accidental, a few suicidal. Both eucalyptus and pennyroyal oil, for example, have been fatal in 1 oz doses (Gurr & Scroggie 1965, Stevenson 1937, Sullivan et al 1979). One of the most toxic essential oils, wormseed, used to be given to children to rid them of worms at a dose of one drop per year of age. Even this dose was sometimes fatal to the child (Wolf 1935). As used in aromatherapy today, essential oils have not caused a single death.

Neurotoxins
Seizures have occurred from ingestion of specific essential oils in moderate doses (Burkhard et al 1989, Millet 1981)

* Hyssop (2 doses of 10 drops)
* Sage (1 dose of 12 drops)
* Thuja (5 doses of 20 drops)

It is evident from these accidents, and from animal tests with both essential oils and constituents, that the active ingredients are the thujones and the pinocamphones. Pinocamphones occur in very few essential oils, wormwood and tansy oils are thujone-rich. Both types of constituent have a GABA antagonistic action, unusual in essential oil constituents, but commonly found in convulsant substances (Hall et al 2004, Höld et al 2000, Höld et al 2002).

Pennyroyal is neurotoxic in overdose, as is wormseed oil (Early 1961, Van Lookeren Campagne 1939).

Camphor, another ketone, is ubiquitous in essential oils. It is also neurotoxic, but is much less potent, and almost all camphor-containing essential oils are safe to use. d-Carvone, administered to mice by i.p. injection was convulsive at 800 mg/kg, but not at lower doses (Gordon et al 1982). Similarly, subcutaneously injected fenchone produced clonic convulsions in mice at a dose of 1,133 mg/kg, but not at 500 mg/kg (Wenzel & Ross 1957). Far from indicating a risk, this suggests that these ketones are not neurotoxic at therapeutic doses.

There is no evidence, nor reason to believe, that other ketones, or essential oils containing them, are neurotoxic as used in essential oil therapy.

Inhaled allergens
A relatively new problem area is that of fragrance materials leading to respiratory distress, mostly in the form of asthma attack. There is no documented evidence of inhaled allergy to any essential oil, the only existing evidence relates to fragrances. A request for information online produced responses from 7 individuals with asthma. All of them said they were very much more susceptible to synthetic fragrances than essential oils. However, one sometimes had problems with lavender oil, another with geranium oil. It appears that both natural and synthetic fragrant materials can exacerbate asthma, and therefore the treatment of this condition by inhalation is an inadvisable option.

Adverse skin reactions
These include sensitization (mostly allergic contact dermatitis (ACD) and phototoxicity) and irritation. Adverse skin reactions are always dependent on the concentration of substance contacting the skin (Johansen et al 1996) as well as other factors, such as skin integrity. Diseased skin has a lower reaction threshold.

Allergic contact dermatitis
It has been said that tea tree oil causes ACD in "about 5%" of those who use it (Stonehouse & Studdiford 2007). However, the evidence does not support this statement. Patch test data using tea tree oil at 5% or 10% in a total of 6,637 dermatitis patients show positive reactions in 0.15-1.8% (Lisi et al 2000, Pirker et al 2003, Rutherford et al 2007, Veien et al 2004). It should be noted that patch testing exaggerates real-world use of a substance (Gerberick et al 2001, Robinson et al 2000) and that a patch test with 5% tea tree oil, for example, is not equivalent to a lotion or oil containing 5% tea tree oil.

In six clinical trials using tea tree oil at either 5% or 10%, there were no allergic reactions among 295 patients, 67 of them with an inflammatory skin condition. Mild reactions were not significantly greater than in placebo groups, and in some cases were less (Caelli et al 2000, Dryden et al 2004, Enshaieh et al 2007, Satchell et al 2002a, Syed et al 1999, Tong et al 1992). However, in clinical trials using the oil at 25%, 50% or 100%, the number of patients with allergic reactions to the oil were 2%, 6% and 8% respectively (Buck et al 1994, Satchell et al 2002b). This highlights the importance of safe concentrations, and suggests a maximum of 10% tea tree oil. However, in some clinical situations, tangible benefits may make a low risk acceptable.

It is also worth noting that Tea tree oil can reduce the oedema and inflammation associated with contact hypersensitivity. This has been attributed to terpinen-4-ol (Brand et al 2002a, 2002b, Koh et al 2002, Khalil et al 2004). Undiluted tea tree oil, but not 5% tea tree oil lotion or placebo, significantly reduced the inflammatory reaction in nickel allergy. This was thought to be due to an effect on the antigen process (Pearce et al 2005). Nickel is the most common cause of skin allergy, followed by fragrance.

Phototoxicity
There is an evidence-based risk from essential oils (such as bergamot) containing furanocoumarins, whether ingested or applied to the skin (Clark & Wilkinson 1998, Cocks and Wilson 1998, Kaddu et al 2001). However, the extrapolation of data from *in vitro* testing undertaken by the SCCP is suspect, since it is not reflected by a high incidence of phototoxic reactions, whether from perfumery, cosmetic or aromatherapy use.

Carcinogens
The essential oil constituents that are generally regarded as carcinogens are:

* methyleugenol
* estragole
* safrole
* asarone

Table 1 is a list of essential oil constituents with some evidence of anticarcinogenic action (references not given).

Methyleugenol (ME) is more widely distributed in essential oils than any of the other constituents. For example, it is found in *Rosa x damascena* oil at 0.5-3.3%. Its presence in any essential oil is regarded by many regulatory agencies as a potential problem and maximum use levels have been set, for example, by the EU. While this is perhaps laudable in the sense of being precautionary, it is reminiscent of the earlier example of acetaldehyde, since methyleugenol is invariably a minor constituent, and is often accompanied by antioxidant, antimutagenic and anticarcinogenic constituents. *Rosa x damascena* oil, for example, also contains 15.7-18.5% geraniol, which has a notable anticarcinogenic action (see Table 2, references not given). Since carcinogenic essential oil constituents act by (a) overwhelming antioxidant systems, and (b) causing DNA damage leading to mutagenesis, the co-presence of antioxidant and antimutagens is highly relevant.

Further, the mathematical exercise undertaken in establishing safety levels for ME include a safety factor of 10 to allow for interspecies differences, i.e. assuming a human susceptibility 10 times greater than that of a rodent. However, this makes no sense, since rodents are much more susceptible than humans to cancers, especially of the liver (Battershill and Fielder 1998, Toth 2001). Estragole, for example, is metabolized more efficiently in human liver, suggesting much reduced toxicity, compared to that in rats (Guenthner and Luo 2001). The setting of arbitrary safety factors is, in any case, unscientific, and not evidence-based.

The presence of carcinogens in essential oils should not be ignored, and this remains an area where risk has not been clearly determined. In this case, the toxicity of whole essential oils should be under consideration, and the case for constituent extrapolation is poor. In fact, essential oils containing carcinogens are sometimes found to have an anticarcinogenic effect in rodents.

Holy basil oil, although it contains two carcinogens, estragole (9.7-12.0%), and methyleugenol (0.2-0.3%) has shown an anticarcinogenic action. It significantly inhibited benzo[*a*]pyrene-induced squamous cell stomach carcinoma in mice (Aruna & Sivaramakrishnan 1996). It also showed significant chemopreventive activity against human mouth epidermal carcinoma and mouse leukaemia cell lines, and was more effective than three of four positive control drugs (Manosroi et al 2005). Holy basil oil also contains 32.0-50.0% eugenol, a potent antioxidant with antigenotoxic and anticarcinogenic potential (references not given).

A further consideration is that genetic differences between individuals affect susceptibility to carcinogens in essential oils (Gardner et al 1997, Jeurissen et al 2004, Rietjens et al 2005)

Essential oils, therefore, have the potential to harm as used in aromatherapy, whether inhaled, taken orally, or applied to the skin. However, only in specific circumstances.

Essential oil quality and integrity
Botanical origin, chemical composition, contamination and degradation of an essential oil all have the potential to affect its performance, and may significantly impact efficacy and safety. Both botanical origin and chemotyping are important because the same common name may be used to describe plants with very different essential oils

Even within the same species and the same chemotype, from the same geographical region, there is variation. This may be due to time of harvest, maturity of plant, environmental conditions, distillation conditions etc. Also, the same species can produce different chemotypes, such as *Ocimum basilicum*, which may predominate in either estragole or linalool. Many other examples exist, such as *Cinnamomum camphora, Melaleuca quinquenervia, Rosmarinus officinalis and Thymus vulgaris.*

And between species, sub-species or varieties of the "same" plant, there can be great variation in major constituents, such as:

Ocimum basilicum   estragole or linalool
Ocimum canum   linalool
Ocimum sanctum   eugenol
Ocimum x citriodorum   citral

Estragole-rich basil oil may be carcinogenic. Similarly, *Acorus calamus* L. var. *angustatus* contains 42-78% of β-asarone, another carcinogen, while *Acorus calamus* L. var. *americanus* contains none.

Chemical integrity
In addition to natural chemical constituents, the integrity of an essential oil may be impacted by adulteration, contamination, or degradation. Common contaminants include biocides and phthalates, and traces of heavy metals have been found in cold-pressed citrus oils.

Monoterpenes and aldehydes are prone to oxidation, notably limonene, α-pinene and citral. Limonene oxidation leads to the formation of more than 20 oxidation products, including limonene 1,2-epoxide and limonene 2-hydroperoxide. Both are potent skin sensitizers (Karlberg et al 1992, 1994). The limonene content of lemon oil decreased from 68.5% to 20.1% in 12 months when the oil was stored at 25°C (77°F) with the cap removed for three minutes every day. However storage at 5°C (41°F), with the cap removed for three minutes once a month, resulted in minimal degradation (Sawamura et al 2004). This highlights the need to protect some essential oils from oxidative degradation. In essential oil therapy, nothing is gained by the ageing of an essential oil.

Is there any benefit from essential oil therapy?
There have been occasional suggestions in the popular press that aromatherapy is no more than placebo, though these claims tend to refer to inhalational essential oil use only. In some studies examining pain or anxiety reduction in a clinical setting, no significant effect from aromatherapy has been seen (Graham et al 2003, Maruzelli et al 2006). However, there is now a small body of clinical evidence that essential oils, whether used orally, topically or by inhalation, can produce results that far exceed placebo (Table 3).

Balancing risk and benefit
Natural complex substances such as essential oils present a special challenge, because they may contain a substance that, when tested as a single chemical, is toxic. Is it reasonable to extrapolate single chemical information to essential oils? One problem with doing this is that the (generally synthetic) chemicals used in testing are often not identical to their natural counterpart, because of (a) isomeric differences in major constituents and (b) the presence of impurities. Another problem is the interaction of the constituents, which is not considered by such extrapolation. However, it is a normal recourse in the regulation of essential oils.

An example of impurities causing problems is coumarin, which has been listed in the EU as a skin allergen. However, it has now been shown that coumarin allergy is due to impurities in the synthetic substance (Vocanson et al 2006).

This approach, the extrapolation of single constituent data to a whole essential oil, is distinct from the "evidence-based" approach, i.e. information deriving from the action of a whole essential oil in a real-world scenario.

Interactions in mixtures
In any mixture of chemicals, there are three possible outcomes (which may differ in the same mixture, depending on what is being measured):

* Synergy
* Additivity
* Antagonism

These interactions, sometimes called matrix effects, may take place on one or more of three levels:

* Between essential oil constituents
* Between essential oils
* Between one or more essential oils and another type of substance

There is a popular belief that any mixture of essential oils is synergistic, or that mixing oils with similar effects will result in synergy. However, synergy and antagonism are counter-intuitive; they are by definition unexpected, and therefore difficult to predict. For example, citral has a zone of inhibition of 22 mm when tested against *Bacillus subtilis*, and myrcene has no effect at all. Yet, mixing myrcene and citral results in an inhibitory zone of 47 mm (Onawumni et al 1984). Antagonism is equally unpredictable (Savelev et al 2003).

In fact mixing two essential oils with a similar action, if that action takes place through the same mechanism, is unlikely to result in synergy. As a general rule, antagonism is less common than synergy when toxicants are mixed (Hodgson et al 1995). Johansen et al (1998a) found that a combination of two fragrance allergens in individuals allergic to both substances had a synergistic effect; the 1:1 mixtures elicited responses as if the doses were 3-4 times higher than those actually used.

The existence of quenching (antagonism in skin allergy) is controversial, but has been demonstrated by Karlberg et al (2001) and by Nilsson et al (2004). There are a number of reports from dermatologists in which patients patch test positive to a single constituent, but not a mixture containing it, for example De Groot et al (1993).

Misinformation and bias
In order to reasonably assess both risks and benefits, it is unfortunately necessary battle a constant stream of misinformation, which comes from many sources:

* The media, who will pick on anything that makes news
* Some doctors (many of whom have an internet presence), who are infected with the scientism bug
* The chemical and pharmaceutical industries, which have a vested interest in promoting synthetics over naturals
* Legislators, who are often far from disinterested parties, and may be heavily biased
* Aromatherapists, who (though perhaps less now than in the past) seem to enjoy promoting myths
* Poor research, which may be unintentional, but can be fodder for all of the above

A collusion of poor research and media hype resulted in a "scare" about tea tree oil and lavender oil being possible causes of pre-pubertal gynecomastia in boys (Henley et al 2007). This report has subsequently been criticized (Dean 2007, Kalyan 2007, Kemper et al 2007, Kurtz 2007) a fact not noted by the media.

Misinformation (aromatherapists)

The essential oils most commonly cited in aromatherapy texts as being contraindicated in hypertension are listed in Table 4. Similar advice is repeated in other books and on many websites, but very little supporting evidence could be found in the scientific literature. The original source for this information appears to be Valnet (1990), first published in French in 1964. In this text, the four essential oils are stated to be hypertensive, and in each case two references are given. One is Caujolle and Franck (1944b), but this is a mistake, since this paper concerns lavender, lavandin and spike lavender oils only, and states that i.v. injection in dogs resulted in a slight reduction in blood pressure, followed by a rapid return to normal. The other reference is a thesis by R. Cazal, published in 1944. Although I was not able to locate a copy of this, it probably concerns similar i.v. injection in dogs, as this seems to have been a standard test at that time. However, examination of other data for these essential oils is revealing.

Injecting dogs i.v. with 1-2 mL of alcohol saturated with hyssop oil resulted in an initial hypotension, followed by hypertension, which was accompanied by convulsions, both lasting 3-4 minutes (Caujolle & Franck 1945b). (It should be noted that intracranial hypertension can lower the seizure threshold.) No relevant data were found for rosemary oil, but some were for two of its constituents, camphor and 1,8-cineole. In cats, camphor caused an initial fall lasting 2-10 minutes, followed by a rise of 8-30 mm Hg above normal and lasting up to 30 minutes, when given intravenously at only 5 mg/kg (Christensen and Lynch 1937). However, 1,8-cineole lowers blood pressure dose-dependently when given i.v. to rats at 0.3-10.0 mg/kg (Lahlou et al 2002). Sage oil also contains varying amounts of camphor and 1,8-cineole, though camphor usually predominates. It produced no increase in blood pressure in dogs, and in some cases a slight fall was observed when ~1 g/kg of alcohol saturated with the oil was given i.v. (Caujolle and Franck 1945a). Interestingly, an intravenously administered aqueous-alcohol extract of sage caused a moderate but prolonged hypotensive effect in cats (Todorov et al 1984). A hypotensive action has also been reported for thyme oil (Kulieva 1980), which is consistent with the calcium antagonist action of thymol and carvacrol, its major constituents (Magyar et al 2004).

Therefore there is some supporting evidence for hyssop oil being hypertensive, but it is not known whether moderate doses would have any effect on human blood pressure. The constituent camphor may have a hypertensive action, but it would be reckless to make any assumptions for camphor-rich oils. The action of rosemary oil may depend on its relative concentrations of 1,8-cineole and camphor, but there is no convincing evidence that it is hypertensive. Both sage and thyme oils appear to be hypotensive, if anything.

As for the other four essential oils in Table 4, in some research published after Davis (1999) temporary hypertension was observed after inhalation of black pepper oil (Haze et al 2002), but this represents a transient psychological effect. White camphor oil is unlikely to raise blood pressure, since it contains very little camphor. There is no evidence that eucalyptus oil increases blood pressure, and we have already seen that its main constituent, 1,8-cineole, is hypotensive. Both peppermint oil and its major constituent, menthol, have a calcium antagonist action, inhibiting calcium uptake in guinea-pig heart muscle, which indicates a hypotensive effect. This correlates with the ability of menthol to dilate systemic blood vessels after intravenous administration, and of peppermint oil to reduce smooth muscle spasm in the gut, both effects being due to calcium antagonism (Grigoleit and Grigoleit 2005, Hawthorn et al 1988, Hills and Aaronson 1991, Rakieten and Rakieten 1957).

There is no evidence that any essential oils have adverse effects on the control of blood pressure in humans. There is no research that shows whether the use of single or blended essential oils can lead to a significant increase in blood pressure during an aromatherapy massage, but this seems unlikely since soft tissue massage itself tends to reduce both systolic and diastolic pressure (Aourell et al 2005, Holland and Pokorny 2001, McNamara et al 2003).

Legislation

The extrapolation + assumption approach is often used in legislation, notably in relation to both carcinogens and skin allergens. There are currently a large number of essential oils impacted by IFRA (Table 5) and these guidelines are likely to be picked up, first by the EU, and subsequently by the CTFA, due to current global harmonization initiatives.

However, it does not make sense to extrapolate (1) from research based on synthetic constituents to their natural equivalents as found in essential oils, and (2) from rodents to humans, with arbitrary safety factors inflating risk many times beyond any known risk.

Unfortunately legislative regulation cannot be relied upon for reliable guidelines, as these are as often as not based on bias or flawed science. Neither can aromatherapy literature be relied upon, as safety guidelines tend to be based on rumor as much as fact.

Ways forward

It is unfortunate that there are no commonly accepted safety guidelines within aromatherapy. This needs to be addressed, and could positively influence the future availability of some essential oils.

In addition to the promotion of existing "non-toxic" chemotypes, it should be possible to encourage the development of, for example, North American calamus oil. A further consideration, already being undertaken by industry, is the removal of undesirable constituents from some essential oils. Whether this is a positive development needs careful consideration.

Summary
* Essential oils in general have the potential to be both harmful and therapeutic.
* Knowing the taxonomy and chemotype of an essential oil is important
* Equally important is the protection of essential oils from chemical degradation
* In spite of the many sources of confusion, it should be possible to develop evidence-based safety guidelines

Resources
Aromatherapy Trade Council
www.a-t-c.org.uk

Cropwatch
www.cropwatch.org

Essential Oil Safety
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References

Aourell M, Skoog M, Carleson J 2005 Effects of Swedish massage on blood pressure. Complementary Therapies in Clinical Practice 11:242-246

Aruna K, Sivaramakrishnan VM Anticarcinogenic effects of the essential oils from cumin, poppy and basil. Phytotherapy Research 10:577-580

Ballard CG, O'Brien JT, Reichelt K et al 2002 Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with Melissa. The Journal of Clinical Psychiatry 63:553-558

Battaglia S 1997 The complete guide to aromatherapy. The Perfect Potion, Virginia, Queensland

Battershill JM, Fielder RJ 1998 Mouse-specific carcinogens: an assessment of hazard and significance for validation of short-term carcinogenicity bioassays in transgenic mice. Human & Experimental Toxicology 17:193-205

Brand C, Townley S L, Finlay-Jones J J et al 2002a Tea tree oil reduces histamine-induced oedema in murine ears. Inflammation Research 51:283-289

Brand C, Grimbaldeston M A, Gamble J R et al 2002b Tea tree oil reduces the swelling associated with the efferent phase of a contact hypersensitivity response. Inflammation Research 51:236-244

Buck DS, Nidorf D M, Addino JG 1994 Comparison of two topical preparations for the treatment of onychomycosis: *Melaleuca alternifolia* (tea tree) oil and clotrimazole. The Journal of Family Practice 38:601-605

Burkhard PR, Burkhard K, Haenggeli C-A et al 1999 Plant-induced seizures: reappearance of an old problem. Journal of Neurology 246:667-670

Caelli M, Porteous J, Carson CF et al 2000 Tea tree oil as an alternative topical decolonization agent for methicillin-resistant *Staphylococcus aureus*. Journal of Hospital Infection 46:236-237

Cappello G, Spezzaferro M, Grossi L et al 2007 Peppermint oil (Mintoil) in the treatment of irritable bowel syndrome: a prospective double blind placebo-controlled randomized trial. Digestive & Liver Disease 39:530-536

Caujolle F, Franck C 1944a Comparative toxicity of thymol and carvacrol. Bull. Soc. Chim. Biol. 26:334-342

Caujolle F, Franck C 1944b Sur l'action pharmacodynamique des essences de lavande, lavandin et aspic [On the pharmacodynamic action of lavender, lavandin and spike lavender oils]. Annales Pharmaceutiques Francaises 2(1):147-148

Christensen BV, Lynch HJ 1937 A comparative study of the pharmacological actions of natural and synthetic camphor. Journal of the American Pharmaceutical Association 26:786-96

Clark SM, Wilkinson SM 1998 Phototoxic contact dermatitis from 5-methoxypsoralen in aromatherapy oil. Contact Dermatitis 38:289-290

Cocks H, Wilson D 1998 Letter to the editor. Burns 24:82

Davis P 1999 Aromatherapy an A-Z. C W Daniel, Saffron Walden

Dean CJ 2007 Prepubertal gynecomastia linked to lavender and tea tree oils. New England Journal of Medicine 356:2543

De Groot AC, van der Kley AM, Bruynzeel DP et al 1993 Frequency of false-negative reactions to the fragrance mix. Contact Dermatitis 28:139-140

Dryden MS, Dailly S, Crouch M 2004 A randomized, controlled trial of tea tree topical preparations versus a standard topical regimen for the clearance of MRSA colonization. Journal of Hospital Infection 56:283-286

Early D F 1961 Pennyroyal: a rare case of epilepsy. Lancet 281:580-581

Enshaieh S, Jooya A, Siadat AH et al 2007 The efficacy of 5% topical tea tree oil gel in mild to moderate acne vulgaris: a randomized, double-blind placebo-controlled study. Indian Journal of Dermatology, Venereology & Leprology 73:22-25

Franchomme P, Pénöel D 1990 L'aromatherapie exactement. Jollois, Limoges

Gardner I, Wakazono H, Bergin P et al 1997 Cytochrome P450 mediated bioactivation of methyleugenol to 1'-hydroxy methyleugenol in Fischer 344 rat and human liver microsomes. Carcinogenesis 18(9):1775-1783

Gerberick GF, Robinson MK, Felter SP et al 2001 Understanding fragrance allergy using an exposure-based risk assessment approach. Contact Dermatitis 45:333-340

Gordon WP, Forte AJ, McMurtry RJ et al 1982 Hepatotoxicity and pulmonary toxicity of pennyroyal oil and its constituent terpenes in the mouse. Toxicology & Applied Pharmacology 65(3):413-424

Graham PH, Browne L, Cox H et al 2003 Inhalation aromatherapy during radiotherapy: results of a placebo-controlled double-blind randomized trial. 21:2372-2376

Grigoleit HG, Grigoleit P 2005 Pharmacology and preclinical pharmacokinetics of peppermint oil. Phytomedicine 12:612-616

Guenthner TM, Luo G 2001 In vestigation of the role of the 2',3'-epoxidation pathway in the bioactivation and genotoxicity of dietary allylbenzene analogs. Toxicology 160:47-58

Gurr FW, Scroggie JG 1965 Eucalyptus oil poisoning treated by dialysis and mannitol infusion. Australian Annals of Medicine 14:238-249

Hall AC, Turcotte CM, Betts BA et al 2004 Modulation of human GABAA and glycine receptor currents by menthol and related monoterpenoids. European Journal of Pharmacology 506:9-16

Han SH, Hur MH, Buckle J et al 2006 Effect of aromatherapy on symptoms of dysmenorrhea in college students: A randomized placebo-controlled clinical trial. Journal of Alternative & Complementary Medicine 12:535-541

Hawthorn M, Ferrante J, Luchowski E et al 1988 The actions of peppermint oil and menthol on calcium channel dependent processes in intestinal, neuronal and cardiac preparations. Alimentary Pharmacology & Therapeutics 2:101-118

Hay IC, Jamieson M, Ormerod AD 1998 Randomized trial of aromatherapy. Successful treatment for alopecia areata. Archives of Dermatology 134:1349-1352

Haze S, Sakai K, Gozu Y 2002 Effects of fragrance inhalation on sympathetic activity in normal adults. Japanese Journal of Pharmacology 90:247-253

Henley V, Lipson N, Korach K S, Bloch C A 2007 Prepubertal gynecomastia linked to lavender and tea tree oils. New England Journal of Medicine 356:479-485

Hills JM, Aaronson PI 1991 The mechanism of action of peppermint oil on gastrointestinal smooth muscle. Gastroenterology 101:55-65

Hodgson E, Ryu DY, Adams N et al 1995 Biphasic responses in synergistic interactions. Toxicology 105:211-216

Höld KM, Sirisoma NS, Ikeda T et al 2000 α-Thujone (the active component of absinthe): γ-aminobutyric acid type A receptor modulation and metabolic detoxification. Proceedings of the National Academy of Sciences 97:3826-3831

Höld KM, Sirisoma NS, Sparks SE et al 2002 Metabolism and mode of action of *cis-* and *trans*-3-pinanones (the active ingredients of hyssop oil). Xenobiotica 32:251-265

Holland B, Pokorny M E 2001 Slow stroke back massage: its effect on patients in a rehabilitation setting. Rehabilitation Nursing 26:182-186

Jeurissen SM, Bogaards JJ, Awad HM et al 2004 Human cytochrome p450 enzyme specificity for bioactivation of safrole to the proximate carcinogen 1'-hydroxysafrole. Chemical Research in Toxicology 17:1245-1250

Johansen JD, Menné T 1995 The fragrance mix and its constituents: a 14-year material. Contact Dermatitis 32:18-23

Johansen JD, Andersen K E, Rastogi S C et al 1996 Threshold responses in cinnamic aldehyde-sensitive subjects: results and methodological aspects. Contact Dermatitis 34:165-171

Kaddu S, Kerl H, Wolf P 2001 Accidental bullous phototoxic reactions to bergamot aromatherapy oil. Journal of the American Academy of Dermatology 45:458-461

Kalyan S 2007 Prepubertal gynecomastia linked to lavender and tea tree oils. New England Journal of Medicine 356:2542

Karlberg A-T, Magnusson K, Nilsson U 1992 Air oxidation of *d*-limonene (the citrus solvent) creates potent allergens. Contact Dermatitis 26:332-340

Karlberg A-T, Shao LP, Nilsson U et al 1994 Hydroperoxides in oxidized *d*-limonene identified as potent contact allergens. Archives of Dermatological Research 286:97-103

Karlberg AT, Nilsson AM, Luthman K et al 2001 Structural analogues inhibit the sensitizing capacity of carvone. Acta Dermato-Venereologica 81:398-402

Kemper KJ, Romm AJ, Gardiner P 2007 Prepubertal gynecomastia linked to lavender and tea tree oils. New England Journal of Medicine 356:241-2542

Khalil Z, Pearce AL, Satkunanathan N et al 2004 Regulation of wheal and flare by tea tree oil: complementary human and rodent studies. Journal of Investigative Dermatology 123:683-690

Koh KJ, Pearce AL, Marshman G et al 2002 Tea tree oil reduces histamine-induced skin inflammation. British Journal of Dermatology 147:1212-1217

Kulieva ZT 1980 [Analgesic, hypotensive and cardiotonic action of the essential oil of thyme growing in Azerbaijan]. Vestnik Akademii Meditsinskikh Nauk SSSR 9:61-63

Kurtz JL 2007 Prepubertal gynecomastia linked to lavender and tea tree oils. New England Journal of Medicine 356:2542

Lahlou S, Figueiredo AF, Magalhães PJ et al 2002 Cardiovascular effects of 1,8-cineole, a terpenoid oxide present in many plant essential oils, in normotensive rats. Canadian Journal of Physiology & Pharmacology 80:1125-1131

Lin PW, Chan WC, Ng BF et al 2007 Efficacy of aromatherapy (*Lavandula angustifolia*) as an intervention for agitated behaviours in Chinese older persons with dementia: a cross-over randomized trial. International Journal of Geriatric Psychiatry 22:405-410

Lisi P, Meligeni L, Pigatto P et al 2000 Prevalenza della sensibilizzazione all'olio essenziale di *Melaleuca*. [The prevalence of sensitivity to *Melaleuca* essential oil.] Italian Annals of Clinical & Experimental Allergological Dermatology 54:141-144

Manosroi J, Dhumtanom P, Manosroi A 2005 Anti-proliferative activity of essential oil extracted from Thai medicinal plants on KB and P388 cell lines. Cancer Letters 235:114-120

McNamara ME, Burnham DC, Smith C et al 2003 The effects of back massage before diagnostic cardiac catheterization. Alternative Therapies in Health & Medicine 9:50-57

Magyar J, Szentandrassy N, Banyasz T et al 2004 Effects of terpenoid phenol derivatives on calcium current in canine and human ventricular cardiomyocytes. European Journal of Pharmacology 487:29-36

May B, Kuntz HD, Kieser M et al 2000 Efficacy and tolerability of a fixed combination of peppermint oil and caraway oil patients suffering from functional dyspepsia. Arzneimittelforschung 46:1149-1153

Millet Y, Jouglard J, Steinmetz MD et al 1981 Toxicity of some essential plant oils. Clinical and experimental study. Clinical Toxicology 18(12):1485-1498

Muzzarelli L, Force M, Sebold M 2006 Aromatherapy and reducing preprocedural anxiety: A controlled prospective study. Gastroenterology Nursing 29:466-471

Nilsson AM, Jonsson C, Luthman K et al 2004 Inhibition of the sensitizing effect of carvone by the addition of non-allergenic compounds. Acta Dermato-Venereologica 84:99-105

Onawunmi GO, Yisak WA, Ogunlana EO 1984 Antibacterial constituents in the essential oil of *Cymbopogon citratus* (DC.) Stapf. Journal of Ethnopharmacology 12:279-286

Pearce AL, Finlay-Jones JJ, Hart PH 2005 Reduction of nickel-induced contact hypersensitivity reactions by topical tea tree oil in humans. Inflammation Research 54:22-30

Pirker C, Hausen BM, Uter W et al 2003 Sensibilisierung auf Teebaumöl in Deutschland und Österreich - Eine multizentrische Studie der Deutschen Kontaktallergiegruppe. [Sensitization to tea tree oil in Germany and Austria. A multicenter study of the German Contact Dermatitis Group]. Journal der Deutschen Dermatologischen Gesellschaft 1:629-634

Rakieten N, Rakieten ML 1957 The effect of *l*-menthol on the systemic blood pressure. Journal of the American Pharmaceutical Association 46(2):82-84

Rietjens IM, Boersma MG, van der Woude H et al 2005a Flavonoids and alkenylbenzenes: mechanisms of mutagenic action and carcinogenic risk. Mutation Research 574:124-138

Robinson MK, Gerberick GF, Ryan CA et al 2000 The importance of exposure estimation in the assessment of skin sensitization risk. Contact Dermatis 42:251-259

Rutherford T, Nixon R, Tam M et al 2007 Allergy to tea tree oil: retrospective review of 41 cases with positive patch tests over 4.5 years. Australasian Journal of Dermatology 48:83-87

Satchell AC, Saurajen A, Bell C et al 2002a Treatment of interdigital tinea pedis with 25% and 50% tea tree oil solution: a randomized, placebo-controlled, blinded study. Australasian Journal of Dermatology 43:175-178

Satchell AC, Saurajen A, Bell C et al 2002b Treatment of dandruff with 5% tea tree oil shampoo. Journal of the American Academy of Dermatology 47:852-855

Savelev S, Okello E, Perry NS et al 2003 Synergistic and antagonistic interactions of anticholinesterase terpenoids in *Salvia lavandulaefolia* essential oil. Pharmacology, Biochemistry & Behaviour 75:661-668

Sawamura M, Son U-S, Choi H-S et al 2004 Compositional changes in commercial lemon essential oil for aromatherapy. The International Journal of Aromatherapy 14:27-36

Seitz HK, Stickel F 2007 Molecular mechanisms of alcohol-mediated carcinogenesis. Nature Reviews. Cancer 7:599-612

Stevenson CS 1937 Oil of wintergreen (methyl salicylate) poisoning. Report of three cases, one with autopsy, and a review of the literature. American Journal of Medical Science 193:772-788

Stonehouse A, Studdiford J 2007 http://www.consultantlive.com/showArticle.jhtml?articleID=201000174

Sullivan JB, Rumack BH, Thomas H et al 1979 Pennyroyal oil poisoning and hepatotoxicity. Journal of the American Medical Association 242:2873-2874

Syed TA, Qureshi ZA, Ali SM et al 1999 Treatment of toenail onychomycosis with 2% butenafine and 5% *Melaleuca alternifolia* (tea tree) oil in cream. Tropical Medicine & International Health 4:284-287

Todorov S, Philianos S, Petkov V et al 1984 Experimental pharmacological study of three species from genus Salvia. Acta Physiologica & Pharmacologica Bulgarica 10(2):13-20

Tong MM, Altman PM, Barnetson RS 1992 Tea tree oil in the treatment of tinea pedis. Australasian Journal of Dermatology 33:145-149

Toth B 2001 Species susceptibilities to chemical carcinogens: a critical appraisal of the roles of genetic and viral agents. In Vivo 15:467-478

Valnet J 1964 Aromathérapie. Librairie Maloine, Paris (English translation: Valnet J 1990 The Practice of Aromatherapy. C W Daniel, Saffron Walden)

Van Lookeren Campagne J 1939 Vergiftiging door oleum chenopodii. Nederlandisch Tijdschrit Voor Geneeskunde 83:5472-5476

Veien NK, Rosner K, Skovgaard GL 2004 Is tea tree oil an important contact allergen? Contact Dermatitis 50:378-379

Vocanson M, Goujon C, Chabeau G et al 2006 The skin allergenic properties of chemicals may depend on contaminants - evidence from studies on coumarin. International Archives of Allergy & Immunology 140:231-238

Wenzel DG, Ross CR 1957 Central stimulating properties of some terpenones. Journal of the American Pharmaceutical Association 46:77-82

Wolf IJ 1935 Fatal poisoning with oil of chenopodium in a negro child with sickle cell anemia. Archives of Pediatrics 52:126-130

Table 1

Essential oil constituents for which there is evidence of anticarcinogenic action

Allyl isothiocyanate
Benzaldehyde
Benzyl isothiocyanate
Bergamottin
α-Cadinol
β-Caryophyllene
Cinnamaldehyde
Costunolide
Coumarin
Diallyl disulphide
β-Elemene
Eugenol
Farnesol
Geraniol
α-Humulene
β-Ionone
cis-Jasmone
Limonene
Menthol
Methoxsalen
Methyl jasmonate
Myristicin
Nerolidol
Perillyl alcohol
Phenylethyl isothiocyanate
α-Santalol
Sclareol
Thymoquinone
ar-Turmerone
Vanillin
Xanthorrizol

Table 2

Geraniol: anticarcinogenic action

Human   pancreatic cancer cells
Human   colon cancer cells

Rat   colon cancer in vivo
Rat   liver cancer in vivo
Rat   breast cancer in vivo
Mouse   skin cancer in vivo
Mouse   leukaemia in vivo

Table 3

Clinical studies with essential oils showing significant effect beyond placebo

Essential oil	Condition/effect	Intervention improvement	Placebo improvement	Reference

Oral

Essential oil	Condition/effect	Intervention improvement	Placebo improvement	Reference
Peppermint	IBS	75%	38%	Capello et al 2007
Peppermint/caraway	Dyspepsia	65%	20%	May et al 2000

Topical (skin condition)

Essential oil	Condition/effect	Intervention improvement	Placebo improvement	Reference
Tea tree	Acne vulgaris	43.6%	12.0%	Enshaieh et al 2007
Tea tree	Dandruff	41%	11%	Satchell et al 2002b
Various	Alopecia areata	44%	15%	Hay et al 1998

Topical/inhalational

Essential oil	Condition/effect	Intervention improvement	Placebo improvement	Reference
Various	Dysmenorrhea	57%	0%	Han et al 2006
Melissa	Dementia/agitation	66%	14%	Ballard et al 2002

Inhalational

Essential oil	Condition/effect	Intervention improvement	Placebo improvement	Reference
Lavender	Dementia/agitation	29%	-1%	Lin et al 2007

Table 4

Essential oils reputed to raise blood pressure

Reference	Valnet 1964	Tisserand 1977	Franchomme & Pénöel 1990	Battaglia 1997	Davis 1999	Pitman 2004
Essential oil						
Black pepper	-	-	-	-	√	-
Camphor	-	√	-	-	-	-
Eucalyptus	-	-	-	-	-	√
Hyssop	√	√	-	√	√	√

Peppermint	-	-	√	-	√	-
Rosemary	√	√	-	√	√	√
Sage	√	-	-	√	√	√
Thyme	√	-	-	√	-	√

Battaglia 1997 p295, Davis 1999 p153, Edwards 1999 p66, Franchomme and Pénöel 1990 p374, Pitman 2004 p343, Valnet 1964 p220, 260, 272, 288

Table 5

Ambrette seed oil
Basil absolute
Basil oil (estragole CT)
Basil oil (holy)
Basil oil (linalool CT)
Bay oil (West Indian)
Bergamot leaf oil
Bergamot peel oil (distilled)
Betel leaf oil
Cabreuva oil
Cananga oil
Cardamon oil
Carnation absolute
Cascarilla oil
Cassia oil
Cassie absolute
Cinnamon bark oil
Cinnamon leaf oil
Cistus oil
Citronella oil
Clove oil
Davana oil
Fenugreek oil
Galangal oil
Geranium oil
Ginger oil
Ginger lily absolute
Grapefruit peel oil
Honey myrtle oil
Horsemint oil
Jasmine absolutes
Laurel leaf oil
Lemon balm oil (Australian)

Lemongrass oils
Lemon basil oil
Lemon leaf oil
Lemon myrtle oil
Lemon tea tree oil
Lemon peel oils
Lemon thyme oil
Lemon verbena oil
Lemon verbena absolute
Lime peel oil (expressed)
Mace oil
Mandarin leaf oil
May chang oil
Melissa oil
Myrtle oil
Nutmeg oil
Orange blossom oil
Orange blossom absolute
Orange leaf oil
Orange peel oil (bitter)
Orange peel oil (sweet)
Palmarosa oil
Pimento berry oil
Pimento leaf oil
Rose absolute
Rose oil
Sandalwood oil (Australian)
Spike lavender oil
Tarragon oil
Tejpat oil
Tolu balsam extract
Tuberose absolute
Vassoura oil
Ylang-ylang absolute
Ylang-ylang oil