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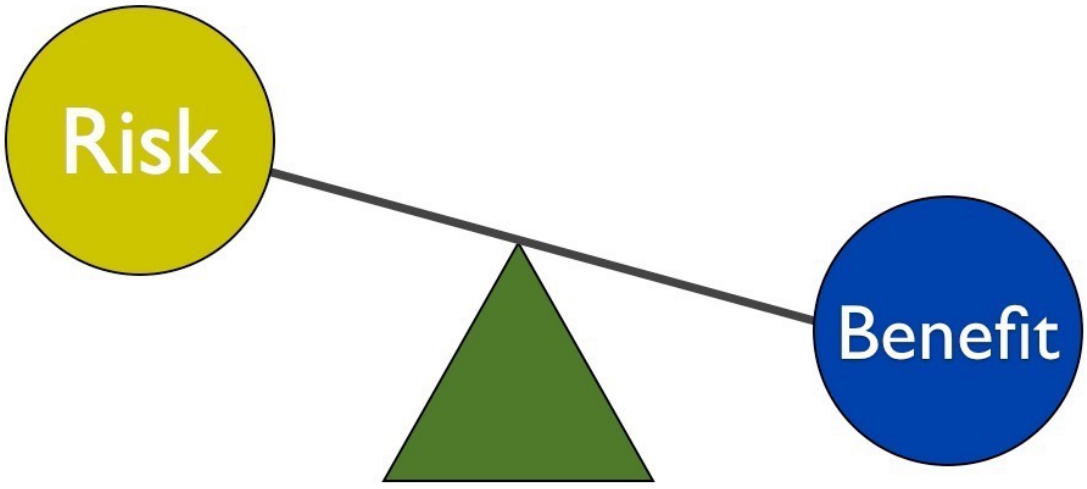
Proof of Safety

Challenges Facing Essential Oil Therapy



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Proof of Safety

Challenges Facing Essential Oil Therapy

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 is "proof of safety"?
* Can essential oils be harmful as used in essential oil therapy?
* Essential oil quality and integrity
* Is there any benefit from essential oil therapy?
* Balancing risk and benefit
* Misinformation & bias
* Legislation

1. What is "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 this 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 absolute safety does not exist, because nothing is absolutely devoid of risk. For example, 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.

Foods containing acetaldehyde

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

2. Can essential oils be harmful as used in essential oil therapy?

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, some 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 one drop per year of age. Even this dose was sometimes fatal to the child (Wolf 1935). However, 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 are only major constituents in hyssop oil. A number of oils are high in thujones, including wormwood and tansy. 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). Thujone, pinocamphone and pulegone (the major constituent of pennyroyal oil) are all ketones.

Camphor, another ketone, is ubiquitous in essential oils. It is also neurotoxic, but is much less potent than the oils mentioned above, 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. In summary, most neurotoxic constituents are ketones, but most ketones (there are many) are not neurotoxic.

Inhaled allergens

A relatively new problem area is that of fragrance ingredients leading to respiratory distress, mostly in the form of asthma attack. However, here 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 entails some risk.

Adverse skin reactions

These come under the categories of 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, and so is more susceptible.

<u>Allergic contact dermatitis</u>

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 allergic reactions in 0.15-1.8% (Lisi et al 2000, Pirker et al 2003, Rutherford et al 2007, Veien et al 2004). Also, 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. The real-world risk of adverse reaction to topically applied tea tree oil at 5% or 10% is probably between 0.01% and 0.1% of people.

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 risk more 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 risk from ingestion is extremely low.

Carcinogens

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

* Methyleugenol
* Estragole
* Safrole
* Asarone

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 arguably 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 8-22% geraniol, which has a notable anticarcinogenic action (see Table 1, 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.

Species	Type of cancer
Human	Pancreatic cancer cells
Human	Colon cancer cells
Rat	Colon cancer in vivo
Rat & mouse	Liver cancer in vitro & in vivo
Rat	Breast cancer in vivo
Mouse	Skin cancer in vivo
Mouse	Leukaemia in vivo

Table 1 Geraniol: antitumoral action

Further, the mathematical exercise undertaken in establishing safety levels for ME include a safety factor of 10 to allow for interspecies differences, i.e. to allow for a human being 10 times more susceptible than a rodent. However, this makes no sense, since the evidence indicates that in fact rodents are much more susceptible than humans to cancers, especially of the liver (Battershill and Fielder 1998, Toth 2001). Also, we know that estragole is metabolized more efficiently in human liver suggesting 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 anticarcinogenac 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

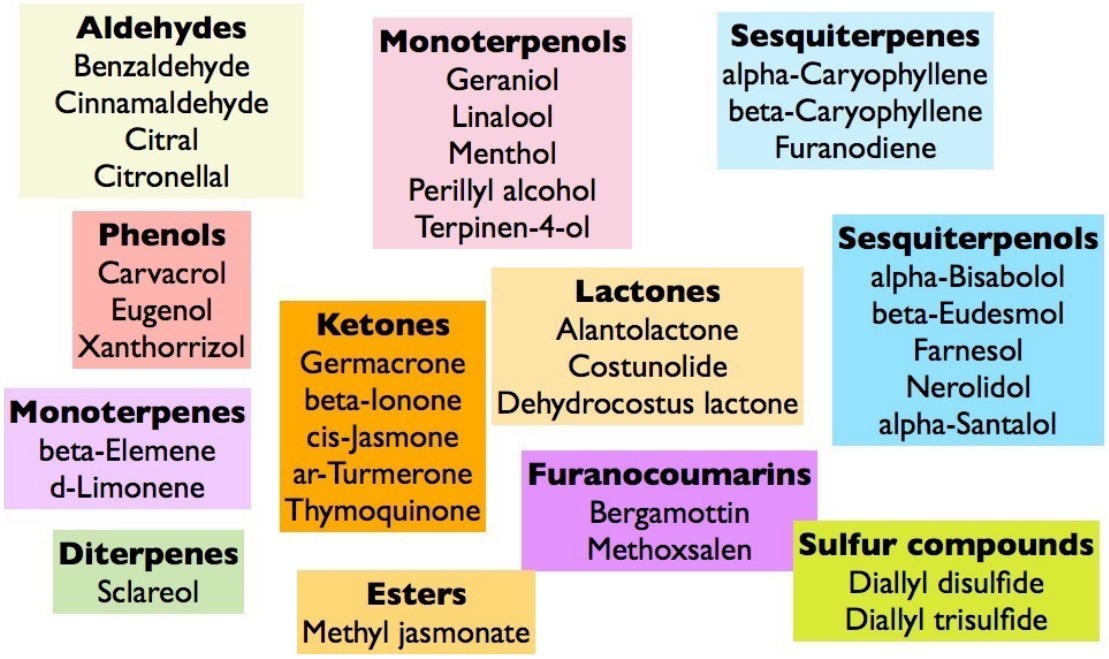

Table 2: List of essential oil constituents with some evidence of antitumoral action (references not given).

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) but there is not space here to explore this.

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

3. Essential oil quality and integrity

Botanical origin, chemical composition, contamination and oxidative degradation of an essential oil all have the potential to affect its performance, and may significantly impact both 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 of essential oils with very different composition, 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 -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. Traces of heavy metals have been found in cold-pressed citrus oils, but in non-harmful amounts.

Monoterpenes and aldehydes are prone to oxidation, notably limonene, *alpha*-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 aging of an essential oil.

4. Is there any benefit from essential oil therapy?

Essential oil	Condition/effect	Intervention improvement	Placebo improvement	Reference
Oral				
Peppermint	Irritable bowel	75%	38%	Capello et al 2007
Peppermint + caraway	Dyspepsia	65%	20%	May et al 2000
Topical (skin condition)				
Tea tree	Acne	43%	12%	Enshaieh et al 2007
Tea tree	Dandruff	41%	11%	Satchell et al 2002b
Various	Alopecia areata	44%	15%	Hay et al 1998
Topical / inhalational				
Various	Menstrual pain	57%	0%	Han et al 2006
Melissa	Dementia/agitation	66%	14%	Ballard et al 2002
Inhalational				
Lavender	Dementia/agitation	29%	-1%	Lin et al 2007

Table 3

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 (see Table 3).

5. 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 and (b) impurities. Another is the interaction of the constituents. However, it is a normal recourse in the regulation of essential oils.

An example of impurities causing problems can be found in 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).

6. 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 often infected with the scientism bug
* Some chiropractors, who think that because they are "doctors" they are automatic essential oil experts
* Multi-level marketing companies, which often make wildly exaggerated claims for essential oils
* 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 continue to promote their own 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 recent "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 (see 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 lowered 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 hyoptensive action has also been reported for thyme oil (Kulieva 1980), which is consistent with the calcium channel 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).

In summary, 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).

	Valnet	Tisserand	Franch. & Penoel	Battaglia	Davis	Pitman
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 4: Oils reputed to raise blood pressure

7. 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 (see Table 5) and these guidelines may be picked up, first by the EU, and subsequently by the CTFA, due to current global harmonization initiatives.

Ambrette seed oil	Cassia oil	Honey myrtle oil	Lime peel oil (expressed)	Pimento leaf oil
Basil absolute	Cassie absolute	Horsemint oil	Mace oil	Rose absolute
Basil oil (estragole CT)	Cinnamon bark oil	Jasmine absolutes	Mandarin leaf oil	Rose oil
Basil oil (holy)	Cinnamon leaf oil	Laurel leaf oil	May chang oil	Sandalwood oil (Australian)
Basil oil (linalool CT)	Cistus oil	Lemon balm oil (Australian)	Melissa oil	Spike lavender oil
Bay oil (West Indian)	Citronella oil	Lemongrass oils	Myrtle oil	Tarragon oil
Bergamot leaf oil	Clove oil	Lemon basil oil	Nutmeg oil	Tejpat oil
Bergamot peel oil (distilled)	Davana oil	Lemon leaf oil	Orange blossom oil	Tolu balsam extract
Betel leaf oil	Fenugreek oil	Lemon myrtle oil	Orange blossom absolute	Tuberose absolute
Cabreuva oil	Galangal oil	Lemon tea tree oil	Orange leaf oil	Vassoura oil
Cananga oil	Geranium oil	Lemon peel oils	Orange peel oil (bitter)	Ylang-ylang absolute
Cardamon oil	Ginger oil	Lemon thyme oil	Orange peel oil (sweet)	Ylang-ylang oil
Carnation absolute	Ginger lily absolute	Lemon verbena oil	Palmarosa oil	
Cascarilla oil	Grapefruit peel oil	Lemon verbena absolute	Pimento berry oil	

Table 5: Essential oils regulated by IFRA

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.

Summary

* Essential oils in general have the potential to be both harmful and therapeutic.
* Knowing the botanical origin 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

It seems 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.

Resources

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

Cropwatch
www.cropwatch.org

Tisserand R, Young R 2014 Essential Oil Safety, 2nd Edition, Churchill Livingstone, Edinburgh
ISBN: 978 0 4430 6241 4

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