Research rebuttal

Estrogenic Activity in Lavender and Tea Tree Oils, Part I

Brian Lawrence examines the research behind an NEJM report’s claim

Brian M. Lawrence, consultant

A report entitled “Prepubertal Gynecomastia Linked to Lavender and Tea Tree Oils” appeared in the New England Journal of Medicine (Henley et al. 2007). The authors concluded that “repeated topical exposure to lavender and tea tree oils probably caused prepubertal gynecomastia in these boys.” To put the context of this paper into perspective it is worthwhile reviewing some information pertinent to this report. In Part I, the following topics will be reviewed:

(a) Biological activity of essential oils and their constituents  
(b) Estrogenic activity  
(c) Estrogenic activity test methods

Biological Activity of Essential Oils and Their Constituents

The biological activity of essential oils has been the subject of a few reviews (Schilcher, 1984; Buchbauer et al. 1993; Lis-Balchin et al. 1998 and Nakatsu et al. 2000). In addition, the safe use of fragrance materials including essential oils and their constituents has been reviewed by Hostyn et al. (1997), Bridges (2002) and Cadby et al. (2002). In these reviews, the international regulations, regulatory bodies and positions of the International Fragrance Association (IFRA), the Research Institute for Fragrance Materials (RIFM) and Cosmetic Toiletry and Fragrance Association (CTFA) are discussed, as are the health concerns including skin penetration, respiratory effects, neurological effects and systemic and environmental effects.

Estrogenic Activity

It is known that many plant derived compounds have the ability to bind to the estrogen receptor. These compounds, reported to possess estrogenic activity, are thought to have beneficial effects; however, it is also possible that they could act as endocrine disruptors (Diel et al. 1999). Publications on the estrogenic activity of essential oils and/or their constituents have appeared in the literature over the past 25 years.

In a review, Albert-Puleo (1980) noted that fennel and anise plants have been used as estrogenic agents for centuries. He postulated that the main active estrogenic agent in the two plants was anethole [(E)-anethole]. Earlier studies have reported the estrogenic activity of both 4-propenylphenol and its dimer (p-anol) (Dodds and Lawson, 1937; Campbell et al. 1938). Gomez and Turner (1938) even reported the mammogenic activity of p-anol in rabbits. The same authors showed that p-anol had an effect on mammary gland growth (1939). Also, Zondek and Bergman (1938) reported that phenyl methyl ethers could be considered as possessing estrogenic activity. Campbell et al. (1938) reported that dianethole exhibited pronounced estrogenic activity. They also postulated that estrogenic activity attributed to
anethole could be due to contamination with polymers of anethole. More recently, Tabanca et al. (2004) reported that several plants contain components that have the capacity to mimic the female hormone estrogen. These compounds are known as phytoestrogens. A review of the types of compounds that possess estrogenic activity has been published by Beckam (1995); the only essential oil noted in this review was anise oil.

Perry et al. (2001) modified the recombinant yeast screen assay and screened a number of Spanish sage oil constituents such as linalool, camphor, α- and β-pinene, 1,8-cineole, geraniol, borneol and thujene (presumed to be α-thujone). They found that only geraniol at high concentrations affected yeast cell growth causing cell lysis. They further postulated that a quantity of geraniol could have been transferred to surrounding cells, thereby affecting their estrogenic activity.

Howes et al. (2002) investigated the potential for estrogenic activity of essential oil constituents. Using the specific recombinant yeast cells bioassay which expresses the human estrogenic receptors, they were able to show that geraniol, neral (as citral), geraniol, nerol and (E)-anethole exhibited estrogenic activity at high concentrations. In contrast, eugenol was shown to possess anti-estrogenic activity. An in vivo study using ovariectomized mice exposed to citral or geraniol revealed that neither compound stimulated characteristic estrogenic responses. The authors concluded that at very high concentrations of essential oil constituents, the potential to express estrogenic activity was quite possible; however, they were uncertain of the biological significance of their findings.

Tabanca et al. (2004) showed that although (E)-anethole may contribute to estrogenic activity in the yeast estrogen screen test (YES test), it was not the
only component of various Pimpinella oils that possessed estrogenic activity according to this test. The authors concluded that a high concentration of the Pimpinella oils studied had the potential ability to react with estrogen receptors. Furthermore, they noted that other in vitro and in vivo studies in combination with the YES test are necessary to categorically understand and explain the estrogenic activity of specific constituents of essential oils.

Kassi et al. (2004) examined the estrogenic activity of aqueous extracts of four Greek aromatic plants. They found that the plant extracts of Sideritis euboea, S. clandestina, Chamomilla recutita and Pimpinella anisum stimulated osteoblastic cell differentiation and exhibited anti-estrogenic effects on breast cancer cells with proliferation of cervical adenocarcinoma (HeLa) cells in the MTT in vitro test. The study could not attribute the biological activity to any component of the plant extracts as no detailed analyses were performed, nor were the estrogenic activities associated with any single component.

Estrogenic Activity Test Methods
A number of test methods have been developed to screen compounds for their estrogenic activity such as (a) receptor binding assay, (b) stimulation of the growth of estrogen sensitive cell (known as the E-screen), (c) stimulation of the transcription of a reporter gene in cell culture (known as the Reporter gene assay), (d) expression of estrogen sensitive gene in cell culture (known as analysis of gene expression), (e) recombinant yeast screen (known as YES assay) and (f) MCF-7 cell proliferation in vitro assay. A summary of the test procedures for tests (a)–(d) can be found in the review by Diel et al. (1999), while the YES assay (e) is described by Routledge et al. (1996) and Tabanca et al. (2004), and the MCF-7 cell proliferation assay (f) is described by Okubo et al. (2003).

References for Part I


Research rebuttal

Estrogenic Activity in Lavender and Tea Tree Oils: Part II

Brian Lawrence examines the research behind a controversial NEJM report

Brian M. Lawrence, consultant

A report entitled “Prepubertal Gynecomastia Linked to Lavender and Tea Tree Oils” appeared in the New England Journal of Medicine (Henley et al. 2007). The authors concluded that “repeated topical exposure to lavender and tea tree oils probably caused prepubertal gynecomastia in these boys.” To put the context of this paper into perspective it is worthwhile reviewing some information pertinent to this report. In the May issue of Perfumer & Flavorist magazine, Lawrence examined: the biological activity of essential oils and their constituents, estrogenic activity and estrogenic activity test methods. In Part II, the following topics will be reviewed:

(a) Lavender oil composition and biological activity
(b) Tea tree oil composition and biological activity
(c) Topical application of essential oils and/or their constituents
(d) Commercially available essential oils and/or their constituents
(e) Safety assessment of essential oils and/or their constituents

Lavender Oil
Lavender oil is available commercially from Australia, Bulgaria, China, France, Moldova, Russia and Ukraine, with Bulgaria and France being the leading producers (Lawrence and Tucker 2004). Each of the above countries grows cultivars specific to their area and France also produces a limited amount of oil from lavender collected from its natural habitat in the rocky, calcareous, sunny mountain slopes of southeastern France between 500 and 1500 m (Upson 2002; Vinot and Bouscary 1962). The chemical composition of lavender oil has been the subject of much study, which itself has been reviewed in depth over the past 30 years (Lawrence 1976, 1978, 1985, 1988, 1993, 1994, 1996, 2000 and 2004). The main constituents found in lavender oils of various origins, and their ISO specifications can be seen in T-1–T-3 (Lawrence 2006). Also, to determine the genuineness of lavender oil it is imperative to measure the enantiomeric distribution of the main constituents of the oil as shown in T-4. From the data found in T-1–T-3, it is readily seen that the two major constituents of lavender oil are linalool and linalyl acetate. A review of the literature reveals that the toxicology and human exposure to linalool and linalyl acetate have been reported by Powers and Beasley (1985), Karlangis (2002), Bickers et al. (2003) and Letizia et al. (2003). Also, Perry et al. (2001) screened linalool for estrogenic activity and found that it possessed antioxidant activity and no estrogenic activity.

Drawing Conclusions
In addition to all the research presented in Parts I and II, Brian M. Lawrence has provided 10 questions and answers to clarify the conclusions that can be drawn from this research study. These Q&A’s were previously published in the March 7 edition of P&Fnow. You can view them now by visiting www.PerfumerFlavorist.com/newsletter/8320427.html. Don’t miss out on being the first to read these important, timely stories—sign up today to receive our free twice-monthly e-newsletter, P&Fnow! Visit www.PerfumerFlavorist.com/newsletter/signup.
whereas van Zyl et al. (2006) could not confirm the antioxidant activity of linalool. The therapeutic uses and biological activity associated with lavender oil have been reported by Buchbauer et al. (1991), Lis-Balchin et al. (1998), Hart and Lis-Balchin (2002), Buchbauer (2002) and Cavanagh and Wilkinson (2002). A few selected interesting studies on lavender oil have been published over the past 15-plus years.

Ludvigson and Rottman (1989) determined that when 12 subjects were exposed to lavender oil vapor, when presented with an arithmetic problem, their cognitive function was adversely affected. Buchbauer et al. (1991) reported an in vivo study with mice that showed a sedative effect after inhalation of lavender oil, linalool and linalyl acetate.

After using lavender oil combined with peanut oil (no percentage given), Jäger et al. (1992) reported that linalool and linalyl acetate from the lavender oil were subcutaneously absorbed within five minutes after massaging the stomach of a male subject. The plasma concentration curve of each component slowly decreased until a minimum was reached after 90 minutes.

The anticonvulsive effects of lavender oil vapor were reported by Yamada et al. (1994).

Buchbauer and Jirovetz (1994) reported that both the motility of mice and a decrease in activity of caffeine-induced overagitated mice occurred on exposure to lavender oil, linalool and linalyl acetate.

Ghelardini et al. (1999) determined that lavender oil, linalool and linalyl acetate possessed local anesthetic activity.

Holmes et al. (2002) determined that when 15 dementia patients were exposed to 2% lavender oil diffused into a treatment room, nine of the patients showed modest improvement in the treatment of agitated behavior.

Tea Tree Oil

Tea tree oil is primarily produced in Australia, where over the years it has become an important item of commerce. It is produced on a plantation scale mainly in northern New South Wales and in

### Percentage composition of commercial lavender oils

<table>
<thead>
<tr>
<th>Compound</th>
<th>French</th>
<th>Moldovan</th>
<th>Ukrainian</th>
<th>Bulgarian</th>
<th>Australian</th>
<th>Indian</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-pinene</td>
<td>t</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0–0.1</td>
</tr>
<tr>
<td>myrcene</td>
<td>0.1</td>
<td>0.5</td>
<td>0.4</td>
<td>0.3</td>
<td>0.3</td>
<td>0.1–0.3</td>
</tr>
<tr>
<td>limonene</td>
<td>t</td>
<td>0.4</td>
<td>0.3</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1–0.2</td>
</tr>
<tr>
<td>1,8-cineole</td>
<td>0.1</td>
<td>1.6</td>
<td>1.5</td>
<td>0.3</td>
<td>t</td>
<td>1.0–1.9</td>
</tr>
<tr>
<td>(Z)-β-ocimene</td>
<td>0.1</td>
<td>1.3</td>
<td>2.4</td>
<td>2.2</td>
<td>0.6</td>
<td>0–0.9</td>
</tr>
<tr>
<td>(E)-β-ocimene</td>
<td>0.3</td>
<td>5.5</td>
<td>4.2</td>
<td>5.5</td>
<td>4.3</td>
<td>0–1.3</td>
</tr>
<tr>
<td>3-octanol</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>2.9</td>
<td>–</td>
</tr>
<tr>
<td>camphor</td>
<td>0.3</td>
<td>0.2</td>
<td>0.3</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>linalool</td>
<td>44.4</td>
<td>34.0</td>
<td>27.5</td>
<td>27.1</td>
<td>39.1</td>
<td>28.2–28.7</td>
</tr>
<tr>
<td>linalyl acetate</td>
<td>41.6</td>
<td>38.6</td>
<td>43.3</td>
<td>42.6</td>
<td>36.2</td>
<td>43.1–50.6</td>
</tr>
<tr>
<td>terpinen-4-ol</td>
<td>1.5</td>
<td>2.0</td>
<td>2.1</td>
<td>4.6</td>
<td>3.0</td>
<td>0.5–0.7</td>
</tr>
<tr>
<td>lavandulyl acetate</td>
<td>3.7</td>
<td>2.5</td>
<td>2.1</td>
<td>4.7</td>
<td>2.5</td>
<td>0.9–1.6</td>
</tr>
<tr>
<td>β-caryophyllene</td>
<td>1.8</td>
<td>3.9</td>
<td>5.9</td>
<td>4.1</td>
<td>2.6</td>
<td>1.0–1.8</td>
</tr>
<tr>
<td>lavandulol</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>0.5</td>
<td>0.4–0.5</td>
</tr>
<tr>
<td>bornol</td>
<td>1.0</td>
<td>0.7</td>
<td>1.0</td>
<td>0.4</td>
<td>0.7</td>
<td>0.3–0.6</td>
</tr>
<tr>
<td>α-terpineol</td>
<td>0.7</td>
<td>1.1</td>
<td>0.6</td>
<td>0.8</td>
<td>0.4</td>
<td>–</td>
</tr>
<tr>
<td>(E)-β-farnesene</td>
<td>0.6</td>
<td>1.7</td>
<td>2.0</td>
<td>2.5</td>
<td>0.4</td>
<td>0.4–0.1</td>
</tr>
</tbody>
</table>

### Comparative percentage composition of French lavender oils

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mailliet</th>
<th>Other cultivars</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-pinene</td>
<td>t–0.7</td>
<td>0.2–1.2</td>
</tr>
<tr>
<td>limonene</td>
<td>t–0.7</td>
<td>0.1–0.6</td>
</tr>
<tr>
<td>1,8-cineole</td>
<td>t–0.2</td>
<td>0.3–1.4</td>
</tr>
<tr>
<td>(Z)-β-ocimene</td>
<td>1.4–2.9</td>
<td>5.0–11.0</td>
</tr>
<tr>
<td>(E)-β-ocimene</td>
<td>0.9–1.4</td>
<td>2.3–5.8</td>
</tr>
<tr>
<td>3-octanol</td>
<td>1.8–3.0</td>
<td>0.9–2.4</td>
</tr>
<tr>
<td>camphor</td>
<td>0.5–0.9</td>
<td>t–0.7</td>
</tr>
<tr>
<td>linalool</td>
<td>29.4–41.6</td>
<td>26.9–49.9</td>
</tr>
<tr>
<td>linalyl acetate</td>
<td>46.7–53.8</td>
<td>36.8–43.0</td>
</tr>
<tr>
<td>β-caryophyllene</td>
<td>2.6–5.1</td>
<td>4.3–7.6</td>
</tr>
<tr>
<td>terpinen-4-ol</td>
<td>t–4.2</td>
<td>3.2–6.4</td>
</tr>
<tr>
<td>lavandulol</td>
<td>t–0.6</td>
<td>0.1–1.6</td>
</tr>
<tr>
<td>lavandulyl acetate</td>
<td>0.3–4.2</td>
<td>0.6–5.9</td>
</tr>
<tr>
<td>α-terpineol</td>
<td>0.1–0.8</td>
<td>0.1–1.4</td>
</tr>
</tbody>
</table>

* t = trace (< 0.1%)*
limited amounts in Queensland. Approximately 3,000 ha (30,000 trees/ha) are currently under tea tree cultivation with an annual oil production of ca. 300 metric tons (Davis 2004). The chemical composition of tea tree oil has been reviewed in depth over the past 30 years (Lawrence 1978, 1989, 1990, 1997, 2001 and 2006).

The main constituents of a typical Australian tea tree oil and the ISO specifications can be seen in T-5 (Lawrence 2006). Also, to assess the genuineness of an oil it is important to determine the enantiomeric distribution of the main constituents of the oil as shown in T-6 (Lawrence 2004; Shellie et al. 2004).

The biological activity and toxicology of tea tree oil have been reviewed by Markham (1999) and Russell (1999), respectively. A few selected interesting studies on tea tree oil and its constituents have been published over the past 20 years.

According to Cabot (1989), tea tree oil is used clinically in Australia for the treatment of Candida albicans infections of the vagina and skin, dandruff, Tinea pedis, varicose ulcers in elderly patients and a broad range of antibacterial infections of the skin.

Carson and Riley (1995) determined the antimicrobial activity of both tea tree oil and its main constituents including terpinen-4-ol, linalool, 1,8-cineole, α-terpineol, etc. The same authors (2001) reviewed the therapeutic and allergic
effects of tea tree oil. Hammer et al. (2002) performed in vitro studies of tea tree oil against dermatophytes and other filamentous fungi. They demonstrated that the oil possessed both inhibitory and fungicidal activity.

Brand et al. (2001) showed that tea tree oil and the water soluble components terpinen-4-ol and α-terpineol may selectively regulate cell function during inflammation, particularly the activity of human monocytes in response to foreign antigens in the skin after topical application. Furthermore, Brand et al. (2002) showed that tea tree oil, α-terpineol and terpinen-4-ol could regulate induced edema formation associated with contact hypersensitivity.

Koh et al. (2002) showed that a histamine-induced inflammation of the skin could be reduced by application of tea tree oil.

Miyazawa and Yamafuji (2005) reported that tea tree oil and terpinen-4-ol could inhibit acetylcholinesterase activity which could make them potentially useful in the treatment of Alzheimer’s disease.

### Topical Application

According to Riviere (1990), for the topical application of a foreign material to the skin, there are three possible fates:

1. Complete absorption into the cutaneous microcirculation
2. The binding of the foreign material either with the stratum corneum (outer skin) or the subcutaneous fat, where it may be released slowly into the capillaries depending upon its structure
3. Fully metabolized by cutaneous enzymes; if the foreign material is volatile then evaporation from the skin surface obviously decreases the subcutaneous absorptive extent (Yourick et al. 1999)

### Commercially Available Essential Oils

Commercially available essential oils are not necessarily 100% genuine to the standard method of isolation of a known

**Enantiomeric distribution of selected tea tree oil constituents**

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Enantiomeric Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1R,5R)-(+)−α-pinene</td>
<td>(90%): (1S,5S)-(−)−α-pinene (10%)</td>
</tr>
<tr>
<td>(1R,5R)-(+)−β-pinene</td>
<td>(67%): (1S,5S)-(−)−β-pinene (33%)</td>
</tr>
<tr>
<td>(1R,5R)-(+)−sabinene</td>
<td>(33%): (1S,5S)-(−)−sabinene (67%)</td>
</tr>
<tr>
<td>(4R)-(+)−α-phellandrene</td>
<td>(41%): (4S)-(−)−α-phellandrene (59%)</td>
</tr>
<tr>
<td>(4R)-(+)−limonene</td>
<td>(&gt; 99.9%): (4S)-(−)−limonene (&lt; 0.1%)</td>
</tr>
<tr>
<td>(1R,4R,5S)-(+)−cis-sabinene hydrate</td>
<td>(&gt; 99.9%): (1S,4R,5S)-(−)−cis-sabinene hydrate (&lt; 0.1%)</td>
</tr>
<tr>
<td>(3S)-(+)−linalool</td>
<td>(68%): (3R)-(−)−linalool (32%)</td>
</tr>
<tr>
<td>(4S)-(+)−terpinen-4-ol</td>
<td>(69%): (4R)-(−)−terpinen-4-ol (31%)</td>
</tr>
<tr>
<td>(4R)-(+)−α-terpineol</td>
<td>(75%): (4S)-(−)−α-terpineol (25%)</td>
</tr>
<tr>
<td>(3S)-(+)-linalool</td>
<td>(68%): (3R)-(-)-linalool (32%)</td>
</tr>
<tr>
<td>(4S)-(+)-terpinen-4-ol</td>
<td>(69%): (4R)-(-)-terpinen-4-ol (31%)</td>
</tr>
<tr>
<td>(4R)-(+)−α-terpineol</td>
<td>(75%): (4S)-(-)-α-terpineol (25%)</td>
</tr>
<tr>
<td>(4R)-(+)−α-pinene</td>
<td>(67%): (1S,5S)-(−)−α-pinene (33%)</td>
</tr>
<tr>
<td>(4R)-(+)−α-terpineol</td>
<td>(75%): (4S)-(−)−α-terpineol (25%)</td>
</tr>
</tbody>
</table>
botanical source within a specific country of origin. According to Lawrence (2002), oils are often standardized or adulterated by the addition of:

(a) A blend of oils from the same botanical source irrespective of geographical origin
(b) An oil or blend of oils with other natural constituents
(c) Oils or fractions of oils of similar composition to the oil
(d) Natural compounds produced enzymatically or from other sources
(e) More than one of the above

The need for knowing how the oil has been stored and for how long is important because upon aging, oil components can and do change, depending on how the oil was stored. Also, if the oil was stored in or exposed to plastic containers, it is common for the oil to leach out one or more of the plasticizers (plastic softeners) such as diethyl phthalate, dibutyl phthalate, benzyl butyl phthalate, dicyclohexyl phthalate, di-2-ethylhexyl phthalate, di-octyl phthalate, di-isononyl phthalate, di-isodecyl phthalate, etc.

The geographic origin of the oil is also important to know as some oils entering commerce have agrochemical residues not found in the same named oil from other geographical origins.

Safety Assessment

Safety assessment of either an essential oil or one or more of its constituents is to determine the potential human exposure to the material (Ford et al. 2000; Paustenbach 2001). To determine exposure it is necessary to know (or measure) the concentration of the material in the product to which a subject is exposed, the amount of product used and the frequency of use. Assuming topical application, then it is important to know not just the dermal exposure but the systemic exposure through absorption.

Before any biological evaluation of a test material, a complete characterization must be determined analytically (Hayes et al, 2007). For an essential oil, it is standard practice to determine both the physico-chemical properties and the chemical composition of the oil. It is critical to know the geographic and botanical origin of the oil, the method of isolation, the age of the oil and its method of storage (Hayes et al. 2007). A material safety data sheet does not act as a substitute for the required laboratory work necessary prior to performing any biological test, particularly in vitro and in vivo tests where microbes, cells or whole animals are involved.

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Lavender, the Genus

Greek plant extracts exhibit selective estrogenic

Prepubertal

Biological

70

(Spanish sage) relevant

In vitro

activities of S. lavandulaefolia

relevant to treatment of Alzheimer’s disease.


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