Tea tree oil: contact allergy and chemical composition

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Summary

In this article, contact allergy to, and the chemical composition of, tea tree oil (TTO) are reviewed. This essential oil is a popular remedy for many skin diseases, and may be used as neat oil or be present in cosmetics, topical pharmaceuticals and household products. Of all essential oils, TTO has caused most (published) allergic reactions since the first cases were reported in 1991. In routine testing, prevalences of positive patch test reactions have ranged from 0.1% to 3.5%. Nearly 100 allergic patients have been described in case reports and case series. The major constituents of commercial TTO are terpinen-4-ol, γ-terpinene, 1,8-cineole, α-terpinene, α-terpineol, *p*-cymene, and α-pinene. Fresh TTO is a weak to moderate sensitizer, but oxidation increases its allergenic potency. The major sensitizers appear to be ascaridole, terpinolene, α-terpinene, 1,2,4-trihydroxymenthane, α-phellandrene, and limonene. The clinical picture of allergic contact dermatitis caused by TTO depends on the products used. Most reactions are caused by the application of pure oil; cosmetics are the culprits in a minority of cases. Patch testing may be performed with 5% oxidized TTO. Co-reactivity to turpentine oil is frequent, and there is an overrepresentation of reactions to fragrance mix I, *Myroxylon pereirae*, colophonium, and other essential oils.

Key words: allergic contact dermatitis; antimicrobial; aromatherapy; chemical composition; contact allergy; essential oil; *Melaleuca alternifolia*; tea tree oil.

Tea tree oil (TTO) [CAS no. 68647-73-4; EG (previously EINECS) 285-377-1] is the volatile oil obtained by distillation from the leaves and terminal branchlets of the narrow-leaf tea tree *Melaleuca alternifolia* (Maiden et Betche) Cheel.* Its INCI names are *M. alternifolia* leaf oil in the EU, and *M. alternifolia* (tea tree) leaf oil in the United States. TTO is perceived by many to be an effective remedy for many skin conditions, and is often applied undiluted. The first report of contact allergy to TTO was published in 1991 (1), and many would follow. In this article, some general information on TTO is presented, the literature on contact allergy is reviewed, and data on the (possible) composition of TTOs are provided. Full literature data on contact allergy to, and the chemical composition of, TTO and nearly 90 other essential oils (including jasmine absolutes) can be found in the book *Essential Oils: Contact Allergy and Chemical Composition* from the authors of this article (2).

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*According to ISO (www.iso.org) criteria laid down in ISO 4730:2004 Essential oil of *Melaleuca*, terpinen-4-ol type, TTO may be obtained from *M. alternifolia* (Maiden et Betche) Cheel, *Melaleuca linariifolia* Smith, and *Melaleuca dissitiflora* F. Mueller. As commercial TTO is produced almost exclusively from *M. alternifolia*, data from oils obtained from the other species are not provided. Their composition, however, bears great resemblance to that of *M. alternifolia* oil.

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The Plant, the Oil, and Their Uses

M. alternifolia is a tall shrub or small tree up to 15 m high with a bushy crown and papery bark. This tree is native to Australia; it occurs naturally in the northern coastal region of New South Wales, bordering Queensland. TTO, which is obtained from the leaves and terminal

branchlets by steam distillation, has been reported to have multiple biological activities, such as bactericidal, antiviral, antifungal, anti-inflammatory, anti-tumoral, analgesic, insecticidal and acaricidal activities (3–7). It is seen by many as a remedy for several skin diseases, including acne, eczema, skin infections such as herpes simplex and warts, wounds, burns, insect bites, dandruff (8), and nail mycoses (9). It is marketed as a 'natural' topical antimicrobial (its antimicrobial effects are well documented) and anti-inflammatory agent (10, 11). In a monograph by the European Medicines Agency (12), TTO was considered to be suitable for the treatment of small superficial wounds and insect bites, small boils ('furuncles and mild acne'), itching and irritation in cases of athlete's foot, and minor inflammation of the oral mucosa (12). The product is present in many different formulations, including pure oil, ointments, wart paint (13), acne treatments (14, 15), and household products such as fabric softeners, detergents, and cleansers (11, 16, 17). The oil is also used in many types of cosmetic products (10, 11, 17), and in aromatherapy for skin diseases, diseases of the respiratory system (e.g. asthma, bronchitis, sinusitis, tuberculosis, and whooping cough), genitourinary diseases (candidiasis, vaginitis, cystitis, and genital pruritus), fever, and infectious diseases such as colds, influenza, and chickenpox (18).

TTO is sold to the public in diluted, highly concentrated, and undiluted forms. However, as products with high concentrations and, especially, aged (oxidized) oils may induce allergic reactions, the European Cosmetics Association COLIPA recommended in 2002 that TTO should not be used in cosmetic products in a way that results in a concentration greater than 1% oil being applied to the skin. Moreover, manufacturers were advised to consider the use of antioxidants and/or specific packaging to minimize exposure to light (19). Useful reviews on various aspects of TTO have been published previously (5, 6, 10, 12, 16, 17, 20–24).

Chemical Composition

TTO is a colourless to pale yellow, clear mobile liquid that has a terpeny, coniferous and minty–camphoraceus odour. The yield of essential oil from the leaves with terminal branches of *M. alternifolia* generally varies from 1.0% to 1.8%. The main country producing this oil is Australia; minor quantities come from China, South Africa, and Vietnam. The chemical composition of TTOs may be extremely variable, depending on parameters such as biomass used (from wild or cultivated trees; only leaves or leaves plus terminal branchlets), chemotype (see below), and mode of production (commercial steam distillation versus preparation by hydrodistillation in the laboratory with a Clevenger-type apparatus).

Table 1. Chemotypes of tea tree oil [adapted from (25)]

	Terpinen-4-ol	1,8-Cineole (eucalyptol)	Terpinolene
Type 1	22–40	0–17	2–6
Type 2	<3	22–44	41–60
Type 3	10–14	34–46	16–24
Type 4	6–14	41–63	0–3
Type 5	<1	72–86	<1
Type 6	<1	65–80	6–14

Numbers are concentrations in % (wt/wt).

Table 2. International Organization for Standardization (ISO) values (%) for tea tree oil[a]

Compound	CAS no.	Minimum	Maximum
Terpinen-4-ol	562-74-3	30.0	48.0
γ-Terpinene	99-85-4	10.0	28.0
1,8-Cineole	470-82-6	tr	15.0
α-Terpinene	99-86-5	5.0	13.0
α-Terpineol	98-55-5	1.5	8.0
p-Cymene	99-87-6	0.5	8.0
α-Pinene	80-56-8	1.0	6.0
Sabinene	3387-41-5	tr	3.5
Aromadendrene	489-39-4	tr	3.0
δ-Cadinene	483-76-1	tr	3.0
Viridiflorene (ledene)	21747-46-6	tr	3.0
Limonene	138-86-3	0.5	1.5
Globulol	489-41-8	tr	1.0
Viridiflorol	552-02-3	tr	1.0

tr, trace.
[a]ISO 4730 Essential oil of melaleuca, terpinen-4-ol type ©ISO 2004; Geneva, Switzerland, www.iso.org.

Chemotypes of TTO

Various plant species are known to have several so-called 'chemotypes'. A clear and widely accepted definition for this well-known phenomenon is lacking. In practice, however, it means that, within a population of one plant species with the same morphological features, groups exist with different compositions of their secondary plant products. This is probably regulated by one or only a few genes (25). The oils produced from the various genotypes are qualitatively very similar; that is, they contain the same spectrum of chemicals, but there are major differences in the quantities of one or several of these. Thus, a specific chemical may be absent or present in trace quantities in one chemotype, and be the dominant component in concentrations of >50% in another. Currently, six chemotypes of *M. alternifolia* leaf oil are commonly distinguished (Table 1).

There is an obvious terpinen-4-ol chemotype (type 1), an obvious terpinolene chemotype (type 2), and an

Table 3. Constituents identified in commercial tea tree oil samples[a]

Constituent	CAS no.	Concentration range (%)	Constituent	CAS no.	Concentration range (%)
Aromadendrene	489-39-4	0.1–2.0	γ-Muurolene	30021-74-0	0–0.3
Bicyclogermacrene	24703-35-3	0–1.2	Myrcene	123-35-3	0.2–4.1
δ-Cadinene	483-76-1	0.2–1.9	α-Phellandrene	99-83-2	0.2–0.6
Calamenene	483-77-2	tr–0.2	β-Phellandrene	555-10-2	tr–5.2
Camphene	79-92-5	tr–0.07	α-Pinene	80-56-8	1.8–9.2
β-Caryophyllene	87-44-5	0.2–1.5	β-Pinene	127-91-3	0.3–1.7
1,8-Cineole	470-82-6	0.5–18.3	Piperitol	491-04-3	0.05–0.3
p-Cymene	99-87-6	0.3–19.4	Sabinene	3387-41-5	0.03–1.3
p-Cymenene	1195-32-0	0.04–3.1	*cis*-Sabinene hydrate	15537-55-0	tr–19.4
α-Eudesmol	473-16-5	0.03–0.5	*trans*-Sabinene hydrate	17699-16-0	0.01–0.3
Globulol	489-41-8	0.02–0.6	Spathulenol	6750-60-3	tr–1.1
α-Gurjunene	489-40-7	0.2–1.0	α-Terpinene	99-86-5	2.3–11.7
cis-3-Hexen-1-ol	928-96-1	0.01–0.07	γ-Terpinene	99-85-4	3.1–23.0
cis-3-Hexenyl acetate	3681-71-8	0–0.02	Terpinen-4-ol	562-74-3	6.2–44.9
α-Humulene	6753-98-6	tr–0.2	α-Terpineol	98-55-5	1.9–4.2
Ledol	577-27-5	0.02–0.3	Terpinolene	586-62-9	0.04–45.7[b]
Limonene	138-86-3	0.5–3.0	α-Thujene	2867-05-2	0.05–1.4
Linalool	78-70-6	0.06–0.8	Viridiflorene (ledene)	21747-46-6	0.3–2.1
p-Menth-2-en-1-ol	619-62-5	0.04–0.7	Viridiflorol	552-02-3	0.08–0.8
Methyl eugenol	93-15-2	0.01–0.4			

CAS, Chemical Abstract Service (www.cas.org).
tr, trace.
[a]Ninety-seven tea tree essential oil samples from Australia, Vietnam, and China ($n = 1$), analysed between 1998 and 2013 (E. Schmidt, unpublished data) (2).
[b]The very high concentration of 45.7% for terpinolene was found in one sample from China only; the median value for all oils was 3.1%.

obvious 1,8-cineole chemotype (type 5). The three remaining chemotypes (3, 4, 6) are dominated by the oil component 1,8-cineole, and are considered to be 1,8-cineole chemotypes that differ in the levels of either terpinen-4-ol or terpinolene present (25). Commercial TTOs are always of the terpinen-4-ol chemotype, type 1.

International Organization for Standardization (ISO) standard

The ISO provides standards with which the mode of production of commercial TTOs and the oils themselves should comply. According to 'ISO 4730:2004, essential oil of *Melaleuca*, terpinen-4-ol type', TTO is obtained by steam distillation of the foliage and terminal branchlets of *M. alternifolia* (Maiden et Betche) Cheel, *M. linariifolia* Smith, and *M. dissitiflora* F. Mueller. However, in practice, commercial TTO is produced from *M. alternifolia* (Maiden and Betche) Cheel (6, 25–27), which is an extremely fast-growing tree and a constantly renewable source of oil (28). The minimum and maximum allowed concentrations of the major components of commercial TTO are shown in Table 2. The chemicals with the highest allowed concentrations are terpinen-4-ol (48.0%), γ-terpinene (28.0%), 1,8-cineole (15.0%), α-terpinene (13.0%), α-terpineol (8.0%), and *p*-cymene (8.0%).

Chemical composition of commercial TTOs (own data)

One of us (E.S.) analysed 97 tea tree essential oil samples from Australia, Vietnam and China ($n = 1$) between 1998 and 2013 by gas chromatography/mass spectrometry (GC/MS) (2). The results are shown in Table 3. The 10 chemicals that had the highest maximum concentrations (concentration range provided) were terpinolene (0.04–45.7%), terpinen-4-ol (6.2–44.9%), γ-terpinene (3.1–23.0%), *p*-cymene (0.3–19.4%), *cis*-sabinene hydrate (trace–19.4%), 1,8-cineole (0.5–18.3%), α-terpinene (2.3–11.7%), α-pinene (1.8–9.2%), β-phellandrene (trace–5.2%), and α-terpineol (1.9–4.2%). The very high concentration of 45.7% for terpinolene was found in one sample from China only; the median terpinolene value for all oils was 3.1%. These data clearly show that not all essential oils can be expected to comply with ISO criteria. The number of identified ingredients is relatively small, as trace constituents (<0.02%), which are not important to the producers and buyers of essential oils, were not quantified and not mentioned in the oils' profiles.

Chemical composition of TTOs from various sources (literature data)

We reviewed the literature on the chemical composition of TTOs up to 11 September 2014 (2), and found nearly

Table 4. Constituents identified in tea tree oils in the literature in concentrations of 1% or higher (2)

Constituent	CAS no.	Highest concentration (%)	Constituent	CAS no.	Highest concentration (%)
δ-Amorphene	189165-79-5	2.0	Oleic acid	112-80-1	1.7
Aromadendrene	489-39-4	2.0	Palustrol	5986-49-2	2.2
Bicyclogermacrene	24703-35-3	6.2	α-Phellandrene	99-83-2	12.2
δ-Cadinene	483-76-1	2.4	β-Phellandrene	555-10-2	1.9
β-Caryophyllene	87-44-5	3.1	2-Phenethyl alcohol	60-12-8	15.3
1,8-Cineole	470-82-6	64.1	α-Pinene	80-56-8	3.4
o-Cymene	527-84-4	4.3	β-Pinene	127-91-3	1.8
p-Cymene	99-87-6	35.3	Sabinene	3387-41-5	1.6
β-Fenchyl alcohol	22627-95-8	3.3	*cis*-Sabinene hydrate	15537-55-0	2.3
Geranial	141-27-5	2.4	Spathulenol	6750-60-3	1.3
Globulol	489-41-8	3.1	α-Terpinene	99-86-5	12.9
α-Guaiene	3691-12-1	1.9	γ-Terpinene	99-85-4	23.2
cis-β-Guaiene	372162-07-7	1.4	Terpinen-4-ol	562-74-3	53.7
Hexanediol	–	4.9	α-Terpineol	98-55-5	11.8
Ledene oxide	882187-44-2	1.2	Terpinolene	586-62-9	45.6
Limonene	138-86-3	7.9	α-Terpinyl acetate	80-26-2	6.0
Linalool	78-70-6	3.2	α-Thujene	2867-05-2	1.7
Longifolene (junipene)	475-20-7	1.3	1,2,4-Trihydroxymenthane	66767-24-6	4.6
2-Methyl-5-decanone	54410-89-8	3.3	Viridiflorene (ledene)	21747-46-6	6.1
Myrcene	123-35-3	2.5	Viridiflorol	552-02-3	1.4
Neodihydrocarveol	18675-33-7	6.3			

50 relevant articles presenting analyses of TTO samples, and three articles reviewing additional analytical investigations (29–31). Analyses were nearly always performed with GC/MS. The majority of analysed TTOs were commercial samples [e.g. (28, 32–35)], and some were laboratory-prepared, usually with a Clevenger-type apparatus [e.g. (4, 36)]. The number of analysed oils ranged from one (in over half of the publications) to 'hundreds' (33). Most samples were (probably) fresh, but some investigators have analysed aged (oxidized) oils (33, 37, 38).

In the TTOs analysed in these studies, over 220 chemicals have been identified. Approximately 55% of these were found in a single reviewed publication only. The compounds that have been found in any study in a concentration of 1% or higher are shown in Table 4. The chemicals that were identified in most samples include (highest concentrations in any study given) 1,8-cineole (64.1%), terpinen-4-ol (53.7%), terpinolene (45.6%), *p*-cymene (35.3%), γ-terpinene (23.2%), α-terpinene (12.9%), and α-terpineol (11.8%). Well-known ingredients of TTOs that were present in high concentrations (>7%) in one or two studies only were α-phellandrene (12.2%) and limonene (7.9%). A rare constituent of TTO found in a high concentration (>7%) in a single study is 2-phenethyl alcohol (15.3%). Full literature data are presented in reference 2. It should be realized that some studies were poorly designed or performed, and that incorrect identifications, especially with trace constituents and certainly in older studies (when analytical methods were far from perfect), are most likely not rare.

Effect of ageing on the composition of TTOs

The composition of TTO changes, particularly in the presence of atmospheric oxygen, but also when the oil is exposed to light, humidity, and higher temperatures. Under these conditions, the antioxidants α-terpinene, γ-terpinene and terpinolene are oxidized to *p*-cymene. Consequently, the levels of α-terpinene, γ-terpinene and terpinolene decrease, whereas the level of *p*-cymene increases up to 10-fold (33, 39). Hence, the concentration of *p*-cymene is a good measure of the oxidative degradation of TTO (38). Oxidation processes also lead to the formation of peroxides, endoperoxides and epoxides such as ascaridole (40). With increasing age, the oil develops a green–brownish colour, the viscosity changes, and the smell becomes turpentine-like. Finally, long thin needles composed of 1,2,4-trihydroxymenthane crystallize (33, 39, 41).

Contact Allergy/Allergic Contact Dermatitis

Contact allergy to, and allergic contact dermatitis caused by, TTO have been reported frequently. In fact, of all essential oils, TTO has caused most (published) allergic reactions since the first cases were reported in 1991 from

Australia, where TTO is produced (1). There are many reports of routine testing; TTO 5% has been part of the screening series of the North American Contact Dermatitis Group (NACDG) since 2003. In groups of consecutive patients suspected of having contact dermatitis, prevalences of up to 3.5% positive patch test reactions have been observed. Undiluted TTO, products with high concentrations and formulations containing 5% TTO can also, possibly depending on the vehicle, induce irritation of the skin/irritant contact dermatitis (10). In this section, data on routine testing, data on patch testing with TTO in groups of selected patients, published case reports, the clinical picture of allergic contact dermatitis caused by TTO, the allergens and patch test procedures are reviewed.

Testing in groups of patients

Routine testing

We found 18 investigations in which consecutive patients suspected of having contact dermatitis were tested with TTO, performed or published between 1997 and 2013. In the more recent ones, the usual test concentration was 5% pet., but, in earlier studies, higher concentrations (up to 100%) were used, i.e., concentrations that are now known to have a high risk of inducing irritant reactions. Most recent investigations were performed by the NACDG. The results of routine testing are shown in Table 5.

Rates of positive reactions have ranged from 0.1% to 3.5%. The highest rates were observed in the Australian studies: 1.8% (51), 2.5% (45, 57), and 3.5% (45). In the NACDG studies (United States and Canada), frequencies ranged from 0.9% to 1.4% (mean 1.1%; median 1.0%) (43, 44, 46, 48, 50). Only two non-Australian studies had scores higher than 2%, one from the United States (47) and the other from the United Kingdom (54). In the US investigation, 2.1% of routinely tested patients reacted to TTO 5%, but many reactions consisted of macular erythema or were weak, and these were counted as positive (47). In the study performed in the United Kingdom, 13 of 550 patients (2.4%) reacted to pure, oxidized TTO, which bears a great risk of false-positive reactions. Indeed, the authors reported a staggering 38% irritant patch test reactions to the test substance (54).

Relevance

In an Australian study, the patch test reactions to TTO of 17 of 41 (41%) patients were considered to be relevant (51). Only 4 of these 17 patients (24%) had used cosmetic products containing TTO (soap, hand cream, face cream, deodorant, and hand lotion; one product each). Two-thirds of the 41 positively reacting patients recalled prior use of TTO, and 20% specified application of neat (100%) TTO (51). In a study of the German Contact Dermatitis Research Group (Germany and Austria), the positive patch test reactions of 20 patients of 36 (56%) were considered to be relevant (56). These patients had used TTO-containing topical products in the (recent) past, leading to blistering and oozing eruptions at the site of application. All had shown ++ or +++ patch test reactions. The other 16, in which relevance was uncertain or absent, had all had a + patch test reaction to TTO only. The causative topical products were not specified (56).

In the NACDG studies, the sum of 'definite' and 'probable' relevance ranged from 20% to 56%; in these studies, no causative products were mentioned (43, 44, 46, 48). In one NACDG study, no relevance data were provided (59).

Both cosmetics (including self-made products) containing TTO and pure oil were causative products in several other studies (53, 54, 58). Occupational allergic contact dermatitis was also reported (54).

Testing in groups of selected patients

In five studies performed between 1996 and 2014, TTO was patch tested in groups of selected patients. Selection criteria included suspicion of cosmetic dermatitis (60), patient-reported cutaneous reactions to products (notably cosmetics) containing botanical ingredients (61), and previous reactivity to ascardidole, a known allergen in TTO (42). The results are shown in Table 6.

The prevalence of reactions to TTO ranged from 1.6% (61) to 41% (60). In the latter study, an early investigation from the United Kingdom, 7 of 17 patients (41%) suspected of having cosmetic dermatitis had a positive patch test reaction to TTO. This unrealistically high percentage can probably be explained by the fact that the patients were tested with pure TTO, which is known to cause many irritant patch test reactions (54). Nevertheless, of these 7 patients, 5 specifically recalled the use of products containing TTO, and a further patient may have been exposed to the oil via aromatherapy (60).

Case reports

Many case reports and case series on allergic contact dermatitis caused by TTO have been reported; details are shown in Table 7.

At least 90 allergic patients have been described. Of the cases in which the products responsible for the allergic reactions were specified, approximately two-thirds were related to pure TTO applied for therapeutic purposes for a variety of skin conditions, including acne, eczema, sunburn, wounds (of any cause), warts, herpes, and fungal infections. There were also some cases caused by topical pharmaceutical preparations containing TTO. Six

Table 5. Results obtained by testing groups of consecutive patients, suspected of having contact dermatitis, with tea tree oil

Years and country	Test concentration and vehicle	Number of patients		Relevance and comments	References
		Tested	Positive (%)		
2011–2013, The Netherlands	5% pet.	221	2 (0.9)	Not relevant. Both patients also reacted to ascaridole, an important allergenic ingredient of tea tree oil	(42)
2011–2012, USA and Canada (NACDG)	5% pet., oxidized	4231	36 (0.9)	Definite + probable relevance: 56%	(43)
2009–2010, USA and Canada (NACDG)	5% pet., oxidized	4299	43 (1.0)	Definite + probable relevance: 50%	(44)
2001–2010, Australia	10% pet.	5087	129 (2.5)	Relevance: 33%	(45)
<2010, Australia	5% pet.	794	28 (3.5)	Relevance: 43% Not absolutely certain that there was no selection	(45)
2007–2008, USA and Canada (NACDG)	5% pet.	5078	71 (1.4)	Definite + probable relevance: 37%	(46)
2000–2007, USA	5% pet.	869	18 (2.1)	Relevance: 100% weak study: (i) high rate of macular erythema and weak reactions; (ii) relevance figures include 'questionable' and 'past' relevance	(47)
2005–2006, USA and Canada (NACDG)	5% pet.	4435	62 (1.4)	Definite + probable relevance: 36%	(48)
<2006 USA and Canada	5% pet.	1603	5 (0.3)	Definite + probable relevance: 20%	(49)
2003–2004, USA and Canada (NACDG)	5% pet.	5137	45 (0.9)	Relevance not stated	(50)
2000–2004, Australia	10% and 5% pet.	2320	41 (1.8)	Relevance: 17/41 (41%); only 4 patients had used cosmetic products containing tea tree oil (soap, hand cream, face cream, deodorant, and hand lotion; one product each); 66% of the 41 patients recalled prior use of tea tree oil, and 20% specified application of neat (100%) tea tree oil	(51)
<2004, USA	5% pet.	1603	5 (0.3)	No details known	(16)
2002–2003, Denmark	10% pet.	377	1 (0.3)	Probably relevant	(52)
1999–2003, Germany	5% DEP, oxidized	2284	21 (0.9)	Relevance: percentage not specified; some patients had used (self-made) cosmetics containing tea tree oil, and others had used the neat oil for eczema, acne, flea bites, and muscle pain, and for evaporation in the sauna or indoors to banish wasps	(53)
2001, UK	Pure, oxidized	550	13 (2.4)	Relevance: 4 relevant, 5 possibly relevant, 4 relevance unknown Two cases of occupational allergy in a beauty therapist and a complementary therapist; other exposures included the use of a shaving gel and children's shampoo; 38% irritant patch test reactions to pure oxidized tea tree oil	(54)
<2000, Italy	5%, 1% and 0.1% pet., undiluted	725 oil	1 (0.1)	Details not known; irritant reactions to undiluted tea tree oil	(55)
1999–2000, Germany and Austria	5% DEP, oxidized	3375	36 (1.1)	Current relevance 56%; range of positive patch test reactions per centre 0–2.3%; co-reactivity to oil of turpentine 39%	(56)
1999, Australia	?	477	12 (2.5)	Relevance not stated. In a group of 12 patients reacting strongly to compound tincture of benzoin, there were 5 (42%) co-reactions to tea tree oil	(57)
1997, France	5%, 10% and 50% in arachis oil, and pure	1216	7 (0.6)	Relevance: the patients used pure oils, creams and hair products containing tea tree oil	(58)

DEP, diethyl phthalate; NACDG, North American Contact Dermatitis Group.

Table 6. Results obtained by testing groups of selected patients with tea tree oil

Years and country	Test concentration and vehicle	Number of patients		Selection of patients (S); Relevance (R); Comments (C)	References
		Tested	Positive (%)		
2014, The Netherlands	5% pet., oxidized	29	4 (13.8)	S: patients with dermatitis who had previously been tested with ascaridole and had a (doubtful) positive or irritant reaction to ascaridole at that time R: no relevance found C: all 4 were also allergic to ascaridole	(42)
2011–2012, Italy	5% pet.	122	2 (1.6)	S: patients who reported adverse cutaneous reactions to products (notably cosmetics) containing botanical ingredients in a questionnaire; they were tested with a 'botanical series' R: both reactions were relevant (not specified)	(61)
2001–2002, Sweden	5% ethanol	1075	29 (2.7)	S: patients referred for routine testing who were willing to participate in a study on cosmetic use and adverse reactions R: not stated	(62)
1998–1999, Australia	Pure and 10% pet.	216	6 (2.8)	S: healthy adult volunteers R: not stated C: the patients were patch tested with 10 different samples; when 'indistinguishable' reactions were counted, the percentage of positive reactions rose to 4.8%; in the subgroup of patients (63%) who had previously come into contact with tea tree oil, the percentages were 4.6% (without 'indistinguishable' reactions) and 7.6% (with such reactions); probably an overestimation	(63)
1996–1997, UK	Pure	17	7 (41)	S: patients suspected of having cosmetic dermatitis R: 6/7 relevant	(60)

patients (2 aromatherapists, a complementary therapist, 2 pedicurists, and a beautician) had occupational allergic contact dermatitis caused by TTO. Thus, approximately three-quarters of all cases are caused by the use of undiluted oil or products with high concentrations, usually applied on damaged skin. Cosmetics are the cause of tea tree allergic contact dermatitis in only 25% of all cases [see also (51) and (53); data provided in Table 5]. Products with low concentrations of TTO appear to induce contact allergy or elicit allergic reactions infrequently. Indeed, of 27 cases of contact dermatitis caused by products with TTO that were reported to the Swedish Medicinal Products Agency, all had a TTO concentration of 2% or higher (91). Nevertheless, the use of shampoos containing TTO may cause eyelid dermatitis in previously sensitized individuals (71).

Positive patch test reactions

In some articles, patients with allergic contact dermatitis caused by other sources co-reacted to TTO; either this had no relevance, or the relevance was not mentioned or was uncertain. Because of the abundance of other literature on TTO, these articles are not specifically mentioned here.

Clinical picture of allergic contact dermatitis caused by TTO

In the majority of cases of sensitization, contact allergy/allergic contact dermatitis is caused by the application of pure oil, usually for therapeutic purposes. This results in localized allergic contact dermatitis at the site of application, which may often be blistering and oozing (56). It may either stay limited or spread, sometimes all over the body (75). The clinical picture of reactions to TTO in cosmetics depends on the product used. The dermatitis is usually less severe, because of lower concentrations of the allergen in the cosmetic products and application to intact skin. Examples include periorbital/eyelid dermatitis caused by soap, cream, and shampoo (65, 71), dermatitis of the beard area caused by shaving oil (65), dermatitis of the face caused by face cream (51), and dermatitis of the face and hands caused by hand lotion (51). Stomatitis has resulted from contact allergy to TTO in a toothpaste (72).

There are several reports of allergic contact dermatitis caused by occupational exposure, for example in aromatherapists (75, 86), a beauty therapist/beautician (54, 89), complementary therapists (54, 66), and a pedicurist (89). In the majority, the hands and/or forearms were affected (54, 66, 86, 89).

Table 7. Case reports of allergic contact dermatitis caused by tea tree oil

Years and country	No. of patients allergic to tea tree oil	Causative products, clinical data, and comments	References
2015, Spain	5	Pure oils	(64)
2013, The Netherlands	2	Soap and cream containing tea tree oil in 1 patient, shaving oil in the second patient, who had the clinical picture of folliculitis barbae; both patients also reacted to ascaridole	(65)
2011, UK	1	Essential oil used by a 'complementary therapist' with contact allergy to many other oils	(66)
2000–2010, Belgium	5	Skin care products; this represented 0.5% of 959 cases of cosmetic allergy where the causal allergen was found	(67)
2000–2009, Belgium	1	Skin care product	(68)
1978–2008, Belgium	2	Topical pharmaceutical preparations	(69)
2007, USA	1	Pure oil used for aromatherapy	(70)
2007, Australia	1	The patient was sensitized by pure oil used for acne, and later developed allergic contact dermatitis of the eyelids from using a tea tree oil-containing shampoo	(71)
2004, Canada	1	Pure oil for aromatherapy; stomatitis from toothpaste	(72)
2004, Germany	1	Pure oil on the face of a 12-year-old boy for a 'minimal skin affection'	(73)
2003, UK	1	Pure oil on a piercing wound; contact allergy may have precipitated linear IgA disease	(74)
2002, UK	1	Pure tea tree oil; the patient was a professional aromatherapist who also reacted to many other essential oils	(75)
2000, UK	1	'Tea tree oil products' used for vulvovaginitis	(76)
2000, Germany	1	No details known	(77)
2000, USA	1	Erythema multiforme-like contact dermatitis (id reaction) from application of pure oil to a wound	(78)
1999, Germany	8	Pure oil in 7 patients for the treatment of eczema, plantar warts, and sunburn	(79)
<1999, Germany	16	Ten patients had used pure oil for skin disorders such as eczema, warts, sunburn, and herpes ($n = 9$), and for 'hygiene and cosmetic purposes ($n = 1$); 1 patient developed dermatitis from shampoo to which pure oil had been added; no data for the other five cases	(80)
1998, Germany	1	Pure oil on psoriasis	(81)
1997, UK	1	Wart paint with tea tree oil	(13)
1997, France	7	Pure oils and cosmetics containing tea tree oil	(58)
1997, Sweden	1	Pure oil on skin irritation	(82)
1997, Germany	2	Pure oil, in 1 patient used on basal cell carcinoma; 1 also reacted to limonene and sweet orange oil	(83)
1996, USA	12	Details not known	(84)
1996, The Netherlands	1	Airborne allergic contact dermatitis from inhalation of aqueous solution of tea tree oil; source of primary sensitization not mentioned	(85)
1995, Norway	1	Hand dermatitis in an aromatherapist, primarily sensitized to lemongrass oil; positive patch test reaction to tea tree oil used at her work. Cajeput was mentioned as synonym, so possibly it was not the oil from *Melaleuca alternifolia*	(86)
1994, Norway	1	Pure oil for acne	(87)
1994, Germany	7	Pure oil on skin disorders such as fungal infection, dog scratches, insect bites, and hand rashes	(88)
1994, The Netherlands	3	Pure oil; occupational contact dermatitis in two pedicurists and a beautician	(89)
1992, The Netherlands	1	Pure oil for the treatment of dermatitis; systemic contact dermatitis after oral administration; the patient co-reacted to 1,8-cineole, an ingredient of the oil	(90)
1991, Australia	2	Undiluted oil; first 2 cases of contact allergy reported	(1)

Allergic contact dermatitis resembling folliculitis barbae (65), erythema multiforme-like contact dermatitis (id) (78) and systemic contact dermatitis after oral administration (90) have rarely been reported. Airborne allergic contact dermatitis caused by inhalation of aqueous solution of TTO has been observed (85), and may be expected with the use of aromatherapy lamps. In 1 patient, contact allergy induced by pure oil on a piercing wound may have precipitated linear IgA disease (74). The majority of patients with allergic contact dermatitis caused by TTO were women.

The allergens in TTO

TTO has been extensively investigated. Its sensitizing potential has been shown in both human and animal experiments. Fresh TTO is a weak (80, 88) to moderate (10, 88, 92–94) sensitizer, but oxidation increases its sensitizing potency (80). Skin sensitization may also be enhanced by irritancy (10). Oil stored in open bottles or in a bottle opened several times undergoes an ageing process. Alterations of the components because of oxidative reactions lead to the formation of peroxides, endoperoxides, and epoxides, usually present in very low amounts, formed by the oxidation of terpinen-4-ol and α-terpinene (95). These chemicals are strong sensitizers (39, 80, 96). Knight and Hausen, in 1994, were the first to look for the sensitizers in TTO by testing allergic patients with a number of the oil's ingredients (88). Of 7 allergic patients, 6 (86%) had positive patch test reactions to limonene, 5 (71%) to α-terpinene and to aromadendrene, 2 (29%) to terpinen-4-ol, and 1 (14%) to *p*-cymene and to α-phellandrene (88). Since then, German investigators in particular have tested a considerable number of patients allergic to TTO with one ingredient, a few ingredients or a battery of its constituents to identify the main sensitizers. The results are shown in Table 8, in which the number of patients allergic to TTO, the test concentration of the oil, and the components reacting in patch testing, with their test concentrations, number of positive reactions, and percentage of positive reactions, are summarized. The results for each individual component in the group of 11 relevant studies (including negative reactions) are shown in Table 9.

The most frequently reacting sensitizers in TTO appear to be ascaridole, terpinolene, α-terpinene [and its oxidation products (96)], 1,2,4-trihydroxymenthane, α-phellandrene, and limonene (Table 9). Other chemicals that may be responsible for TTO allergy, albeit less frequently (<16%), include myrcene, aromadendrene, D-carvone, L-carvone, terpinen-4-ol, viridiflorene, and, rarely (<5%), sabinene, 1,8-cineole, and *p*-cymene. The TTO components α-pinene, β-pinene, γ-terpinene and α-terpineol have thus far not been identified as sensitizers in TTO (Table 9). It should be appreciated, however, that, with the exception of α-pinene, these chemicals have been tested in a only few patients allergic to TTO. Most of the sensitizers have been found in low concentrations or not at all in commercial TTOs; for some (e.g. ascaridole, which is formed during the oxidation of TTO, and 1,2,4-trihydroxymenthane, which is formed during the ageing process), this can be explained by the fact that these were fresh oil samples (Table 4).

Most positive patch test reactions to TTO are probably result from sensitization to the oil itself. However, in some cases, they may possibly reflect prior sensitization to an ingredient of the oil. Thus, of 14 patients with occupational contact dermatitis caused by D-limonene who were patch tested with TTO 5% pet., 5 (36%) had a positive ($n=4$) or doubtful positive ($n=1$) reaction to TTO, although they denied having prior contact with it. This may indicate that previous contact allergy to limonene can result in a positive patch test reaction to TTO (59). In line with this, some authors have suggested that reactions to limonene may be the result of presensitization to fragrances, rather than being caused by the use of TTO (80).

Patch testing with TTO

Indication

Patch testing with TTO is indicated when the history of the patient suggests an allergic reaction to the oil or products containing it. In the majority of cases, this will probably be the pure oil, as neither the history nor the clinical picture will alert the clinician to reactions to TTO in, for example, cosmetics, pharmaceutical products, or household products. Preferably, the TTO-containing product used by the patient should be patch tested at a dilution of 5–10% TTO in an appropriate vehicle such as pet. Concentrations up to 25% may have little irritancy potential (92), but the use of higher concentrations may result in extreme patch test reactions.

Oxidized TTO 5% in pet. is available as a patch test substance from Chemotechnique (www.chemotechnique.se) and from Allergeaze (www.allergeaze.com). The prevalence of positive reactions to TTO in consecutive patients in most countries does not warrant its addition to the baseline series. In Australia, however, inclusion seems to be indicated, and has, indeed, recently been recommended (45), as routine testing has yielded frequencies of sensitization ranging from 1.8% to 3.5% (45, 51, 57). It is unknown whether the inclusion of TTO in any additional series will frequently result in unsuspected currently relevant positive patch test reactions, but this is doubtful. Of

Table 8. Testing with ingredients in patients with positive patch test reactions to tea tree oil

Years and country	No. allergic to tea tree oil (test concentration/vehicle)	Positively reacting ingredients, test concentration and vehicle, numbers positive, percentage positive (in parentheses), and comments	References
2011–2013, The Netherlands	6 (5% pet.)	All reacted to ascaridole 1% and/or 2% and/or 5% in pet.	(42)
2009–2013, Spain	4 (5% pet. and pure)	All reacted to oxidized D-limonene (concentration/vehicle unknown)	(97)
1999–2003, Germany	20 (5% DEP)	Terpinolene 5% DEP, n = 17 (85%); ascaridole 5% DEP, n = 15 (75%); α-terpinene 5% DEP, n = 16 (80%); 1,2,4-trihydroxymenthane 5% pet., n = 13 (65%); α-phellandrene 5% DEP, n = 7 (35%); D-limonene 5% DEP, n = 11 (55%); myrcene 5% DEP, n = 7 (35%); viridiflorene 5% DEP, n = 1 (5%); D-carvone 5% DEP, n = 4 (20%); L-carvone 5% DEP, n = 4 (20%); aromadendrene 5% DEP, n = 1 (5%); sabinene 5% DEP, n = 2 (10%); terpinen-4-ol 5% DEP, n = 1 (5%)	(53)
2000, Germany	8 (20% olive oil)	Terpinolene 10% aq., n = 7 (88%); ascaridole (5% aq.), n = 7 (88%); α-terpinene 5% aq., n = 6 (75%); α-phellandrene 5% aq., n = 5 (63%); 1,2,4-trihydroxymenthane 5% pet., n = 2 (25%); D-carvone (5% aq.), n = 1 (13%); terpinen-4-ol 10% aq., n = 1 (13%)	(79)
2000, Germany	15 (test concentration/vehicle not specified)	All were tested with 1,2,4-dihydroxymenthane, and 11 (73%) reacted positively	(39)
1999–2000, Germany and Austria	10 (5% DEP)	Terpinolene 10% DEP, n == 10 (100%); ascaridole 5% DEP, n = 10 (100%); α-terpinene 5% DEP, n = 10 (100%); 1,2,4-trihydroxymenthane 5% DEP, n = 9 (90%); α-phellandrene 5% DEP, n = 6 (60%); D-limonene 5% DEP, n = 4 (40%); myrcene 5% DEP, n = 1 (10%); viridiflorene 5% DEP, n = 1 (10%)	(56)
1999, Germany	16 (test vehicle not mentioned)[a]	Terpinolene 10%, n = 16 (100%); ascaridole 5%, n = 12 (75%); α-terpinene 5%, n = 11 (69%); 1,2,4-trihydroxymenthane 5%, n = 8 (50%); α-phellandrene 5%, n = 5 (31%); myrcene 5%, n = 2 (13%); D-limonene 5%, n = 1 (6%); viridiflorene 5%, n = 1 (6%)	(80)
1998, Germany	1 (concentration/vehicle ?)	1 reaction to ascaridole; article not read	(40)
1997, Australia	3 (varying test concentrations)	α-Terpinene, n = 1; 3 patients reacted to a sesquiterpenoid hydrocarbon fraction and sesquiterpenoid mixed with paraffin to obtain a concentration as in 25% tea tree oil	(92, 93)
1994, Germany	7 (1% solution)	D-Limonene 1% ethanol, n = 6 (86%); α-terpinene 1% ethanol, n = 5 (71%); aromadendrene 1% ethanol, n = 5 (71%); terpinen-4-ol 1% and 5% ethanol, n = 2 (29%); *p*-cymene 1% ethanol, n = 1 (14%); α-phellandrene 1% ethanol, n = 1 (14%)	(88)
1992, The Netherlands	1 (pure)	1,8-Cineole (eucalyptol) 5% pet., n = 1 (100%)	(90)

DEP, diethyl phthalate.
[a]Test concentrations were probably in DEP for all allergens except 1,2,4-trihydroxymenthane, which was tested in pet. (53).

the ingredients of TTO that have caused contact allergy, only limonene and carvone are available as commercial patch test materials. For testing with the important sensitizer ascaridole, a test concentration of 2% has been recommended (42). Higher concentrations may reveal more cases of sensitization, but also result in some 10% doubtful and 10% irritant reactions (42).

Co-reactivity

Oil of turpentine. There appears to be frequent co-reactivity to oil of turpentine in patients reacting to TTO. The German Contact Dermatitis Research Group tested 3375 consecutive patients suspected of having contact dermatitis in 1999 and 2000 in 11 clinics in Germany and Austria (56). There were 36 (1.1%) positive reactions to TTO. Fourteen of these patients (39%) co-reacted to oil of turpentine 10% pet., which is part of the baseline series in these countries (56). In another German study (80), concomitant reactions to oil of turpentine were seen in 7 of 16 (44%) patients allergic to TTO, and co-reactivity was also observed in a case report (73).

A commercial oil of turpentine test substance used by the members of the German Contact Dermatitis Research Group contained 72% α-pinene, 15% β-pinene, 5% dipentene (limonene), 2% caryophyllene, 1% camphene, 1% myrcene, 1% longifolene, 0.1% carenes, and 3% unidentified components, with a peroxide degree of 30% (98).

Table 9. Summary of patch testing with ingredients of tea tree oil

	Number of patients per study				Total number of patients in 11 studies			
Tea tree oil component	Tested	Positive	% Positive	References	Tested	Positive	% Positive	Range positive (%)
Ascaridole	20	15	75	(53)	61	51	84	75–100
	10	10	100	(56)				
	16	12	75	(80)				
	8	7	88	(79)				
	6	6	100	(42)				
	1	1	100	(40)				
Terpinolene	20	17	85	(53)	64	50	78	0–100
	16	16	100	(80)				
	10	10	100	(56)				
	8	7	88	(79)				
	7	0	0	(88)				
	3	0	0	(93)				
α-Terpinene	20	16	80	(53)	64	49	77	33–100
	16	11	69	(80)				
	10	10	100	(56)				
	8	6	75	(79)				
	7	5	71	(88)				
	3	1	33	(93)				
1,2,4-Trihydroxymenthane	20	13	65	(53)	69	43	62	25–90
	16	8	50	(80)				
	15	11	73%	(39)				
	10	9	90	(56)				
	8	2	25	(79)				
α-Phellandrene	20	7	35	(53)	54	23	43	31–63
	16	5	31	(80)				
	10	6	60	(56)				
	8	5	63	(79)				
Limonene	3	0	0	(93)	73	29	40	0–100
D-Limonene	20	11	55	(53)				
	16	1	6	(80)				
	10	4	40	(56)				
	8	0	0	(79)				
	7	6	86	(88)				
	5	3	60	(64)				
D-Limonene (oxidized)	4	4	100	(97)				
Myrcene	20	7	35	(53)	61	10	16	0–35
	16	2	13	(80)				
	10	1	10	(56)				
	8	0	0	(79)				
	7	0	0	(88)				
Aromadendrene	20	1	5	(53)	61	6	10	0–71
	16	0	0	(80)				
	10	0	0	(56)				
	8	0	0	(79)				
	7	5	71	(88)				
D-Carvone	20	4	20	(53)	61	5	8	0–20
	16	0	0	(80)				
	10	0	0	(56)				
	8	1	13	(79)				
	7	0	0	(88)				
L-Carvone	20	4	20	(53)	54	4	7	0–20
	16	0	0	(80)				
	10	0	0	(56)				
	8	0	0	(79)				

Table 9. Continued

	Number of patients per study				Total number of patients in 11 studies			
Tea tree oil component	Tested	Positive	% Positive	References	Tested	Positive	% Positive	Range positive (%)
Terpinen-4-ol	20	1	5	(53)	64	4	6	0–29
	16	0	0	(80)				
	10	0	0	(56)				
	8	1	13	(79)				
	7	2	29	(88)				
	3	0	0	(93)				
Viridiflorene	20	1	5	(53)	54	3	6	0–10
	16	1	6	(80)				
	10	1	10	(56)				
	8	0	0	(79)				
Sabinene	20	2	10	(53)	38	2	5	0–10
	10	0	0	(56)				
	8	0	0	(79)				
1,8-Cineole (eucalyptol)	20	0	0	(53)	62	1	2	0–100
	16	0	0	(80)				
	10	0	0	(56)				
	8	0	0	(79)				
	7	0	0	(88)				
	1	1	100	(90)				
p-Cymene	20	0	0	(53)	64	1	2	0–14
	16	0	0	(80)				
	10	0	0	(56)				
	8	0	0	(79)				
	7	1	14	(88)				
	3	0	0	(93)				
α-Pinene	20	0	0	(53)	64	0	0	0
	16	0	0	(80)				
	10	0	0	(56)				
	8	0	0	(79)				
	7	0	0	(88)				
	3	0	0	(93)				
β-Pinene	3	0	0	(93)	3	0	0	0
γ-Terpinene	3	0	0	(93)	3	0	0	0
α-Terpineol	7	0	0	(88)	10	0	0	0
	3	0	0	(93)				

Ingredients of these preparations that have been found as sensitizers in TTO include limonene and myrcene (Table 9). In the second half of the 1990s, a sudden increase in the prevalence of positive patch test reactions to oil of turpentine was noticed (98). It has been suggested that this can partly be explained by primary TTO sensitization (56), oil of turpentine reacting to common allergenic ingredients, or cross-reacting substances. Indeed, of 16 turpentine-positive patients who denied contact with turpentine, and who were tested with their own TTO preparations, 10 (63%) showed positive patch test reactions to TTO (98).

Other co-reacting substances. In patients allergic to TTO, co-reactions to fragrance mix I (58, 66, 75, 80, 85, 86, 89), *Myroxylon pereirae* (balsam of Peru) (66, 75, 78, 80, 89), colophonium (rosin) (58, 74, 75, 78–80, 85, 87, 89) and one or more essential oils (56, 66, 75, 76, 80, 85, 86, 89) have been observed regularly. Although there appears to be an overrepresentation, the data are insufficient to show whether the frequencies of co-reactivity are significantly increased, and, if so, whether they are attributable to concomitant sensitization, cross-reactivity, or pseudo-cross-reactivity (common allergenic ingredients). However, the association between TTO and oil of turpentine reactions seems to be clear (~40% co-reactivity to oil of turpentine (56, 80). In turn, turpentine-sensitive patients react significantly more frequently to the fragrance mix (46% of the patients versus 9.4% of turpentine-negative

patients), to *Myroxylon pereirae* (29% versus 7% of turpentine-negative patients), and to colophonium (23% versus 3% of turpentine-negative patients) (98).

In a group of 12 patients reacting to compound tincture of benzoin [benzoin 10%, aloe 2%, styrax 8%, *Myroxylon balsamum* (balsam of Tolu) 4% in 95% ethanol], 5 (42%) co-reacted to TTO. The number of TTO-allergic patients who also reacted to compound tincture of benzoin was not mentioned (57). Co-reactivity to TTO in a tincture of benzoin-sensitive patient was also mentioned in (99). An aromatherapist allergic to TTO and many other essential oils also reacted to benzoin (86).

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