Is Cineole Detrimental to Tea Tree Oil?

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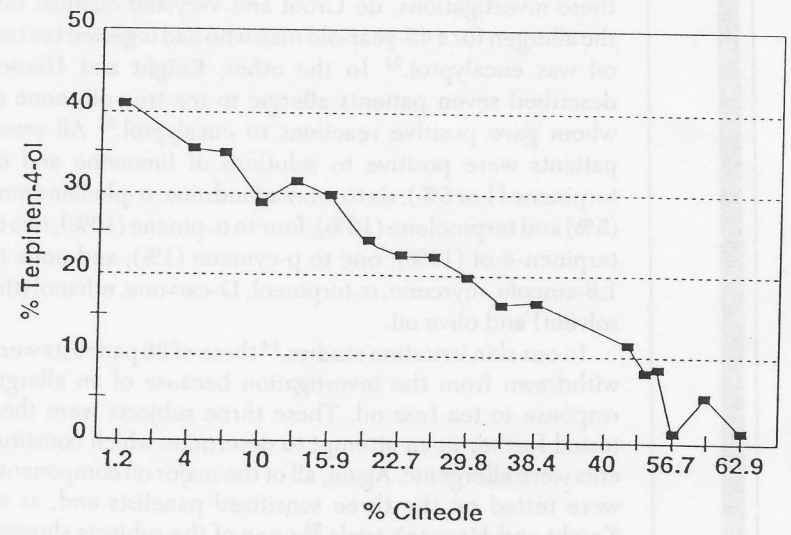
During the last ten years, sales of essential oil from the Australian tea tree (*Melaleuca alternifolia*) have increased from around 8 tons[1] to 150-200 tonnes per annum.[2-5] Many buyers consider 1,8-cineole (eucalyptol) concentration to be the most important quality criterion for their purchases. The available data does not support the view that low cineole (0-5%) tea tree oils are superior to moderate cineole (5-15%) oils. This paper evaluates the claims about cineole in tea tree oil and reviews the results of recent skin irritancy and bioactivity investigations which show that cineole is neither an irritant nor an antagonist. Reasons for this industry misconception are suggested.

Cineole Levels

Previous literature: One year after being raised to species rank from *Melaleuca linariifolia* var. *alternifolia*,[6] *M. alternifolia* essential oil was investigated and reported to contain 6-8% 1,8-cineole.[7] The existence of chemical varieties with a higher concentration of cineole (termed "physiological forms") soon became evident, prompting investigations which established three varieties based on cineole content: Type (6-14%), Var. A (31-41%) and Var. B (54-64%).[8] It must be remembered that these cineole determinations were based on o-cresol methods. With the advent of gas chromatography (GC) and the analysis of statistically significant numbers of samples, these varieties tended to merge as cineole concentrations of 0.5-86.3% were discovered.[9] The GC analysis of thousands of samples, first at the Museum of Applied Arts and Sciences, and then at NSW agriculture laboratories (the Biological and Chemical Research Institute and the Wollongbar Agricultural Institute), indicated that cineole concentration was inversely proportional to terpinen-4-ol concentration. Hence, as cineole concentration increases, terpinen-4-ol concentration decreases (Figure 1).

Standards: It was with this variation in mind that Standards Australia revised the 1967 Australian tea tree oil standard,[10] which specified only physical constants, to include a gas chromatographic maximum of 15% for cineole and a minimum of 30% for terpinen-4-ol, the active ingredient.[11] This restriction was aimed at excluding the undesirable higher cineole concentration chemical varieties of



% Cineole	% Terpinen-4-ol
1.2	40.4
4.0	35.8
7.1	35.0
10.0	29.0
13.0	31.9
15.9	30.0
20.0	23.6
22.7	22.2
26.2	22.0
29.8	20.0
34.4	17.4
38.4	17.8
44.1	12.4
49.0	8.9
51.7	9.4
56.7	0.9
60.2	5.3
62.9	0.9

Figure 1. The percentages of cineole and terpinen-4-ol in typical tea tree oils

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M. alternifolia (Var. A and Var. B), which have terpinen-4-ol concentrations below 30%. The International Standards Organization (ISO) used this Australian Standard as a basis for draft standard ISO/DIS 4730 Oil of Melaleuca-Terpinen-4-ol type.[12] This was adopted in 1994, with minor changes by the ISO TC54 Committee, as the International Standard. This Standard includes a chromatographic profile that specifies ranges of concentration for 14 significant oil constituents. 1,8-Cineole has to have a concentration in the 0-15% range.

Market: Buyers of tea tree oil have assumed that since cineole must be present at 15% or less, it is an undesirable constituent in the oil. Hence, oils with lower percentages of cineole have been preferred on the market. When asked why, very few people reply correctly that if cineole is low in concentration, then terpinen-4-ol, the active ingredient, is high, and hence the oil is more active. Some reply that cineole is a skin irritant or that oils with higher cineole concentrations are not as active. Experimental work does not support the first of these explanations, and the second is only true if terpinen-4-ol is reduced in concentration below approximately 30% because of the presence of more cineole.

Skin Irritancy

The fact that cineole and eucalyptus oil have been used in chest rubs and other dermal application products for many years without adverse effects is, in itself, evidence that cineole is not a skin irritant. This has been verified by studies on animal and human subjects with neat and 16% preparations, respectively.[13] Full-strength eucalyptol was nonirritating to both intact and abraded rabbit skin for 24 hours under occlusion. A 16% formulation in petrolatum was also nonirritating on 25 human subjects after a 48-hour closed patch test. Consequently, it is unlikely that cineole in tea tree oil is responsible for skin irritancy.

To confirm this, and to assess any possible synergistic effect between cineole and tea tree oil constituents, we conducted further clinical studies.[14] Pure 1,8-cineole in concentrations of 0.0, 3.8, 8.0, 12.0, 16.0, 19.9, 24.0 and 28.1% in soft white paraffin did not produce skin irritancy when tested by occlusive patch on 25 human subjects. Similarly, eight tea tree oil preparations containing 1.5, 3.1, 5.7, 10.4, 15.0, 18.4, 24.4 and 28.8% cineole did not produce skin irritancy when tested as 25% formulations in soft white paraffin on 25 human subjects.

These results negate statements such as "cineole is a mucous membrane and skin irritant,"[15] "it is generally accepted that cineole is a skin irritant,"[16] "cineole is very low to help avoid irritation as well as increasing the expected effect"[17] and "1,8-cineole, reputedly a skin irritant."[18] Uncorroborated statements such as these have been repeated to the detriment of the essential oil industry.

Sensitization

Allergic responses are sometimes confused with irritancy. Reactions are classed as allergic rather than irritant when they show erythema (redness) with edema (swelling) and itching. The skin irritancy studies reported by Opdyke[13] also showed no sensitization for 25 volunteers tested with 16% eucalyptol in petrolatum. Eucalyptus oil caused sensitivity in only 3 out of 200 dermatitis patients[19] in investigations reported by Rudzki et al.[20]

Contact dermatitis reactions to tea tree oil have been reported. In some cases these were confirmed by positive patch tests, and on two occasions the major tea tree oil constituents were independently investigated. In one of these investigations, de Groot and Weyland claimed that the allergen for a 45-year-old man who had ingested tea tree oil was eucalyptol.[21] In the other, Knight and Hausen described seven patients allergic to tea tree oil, none of whom gave positive reactions to eucalyptol.[22] All seven patients were positive to solutions of limonene and α-terpinene (1 or 5%); six to aromadendrene, α-phellandrene (5%) and terpinolene (10%); four to α-pinene (10%); two to terpinen-4-ol (10%); one to p-cymene (1%); and none to 1,8-cineole, myrcene, α-terpineol, D-carvone, ethanol (the solvent) and olive oil.

In our skin irritation studies,[14] three of 28 panelists were withdrawn from the investigation because of an allergic response to tea tree oil. These three subjects were then tested further in an attempt to determine which constituents were allergenic. Again, all of the major oil components were tested on the three sensitized panelists and, as in Knight and Hausen's trials,[22] none of the subjects showed allergic response to cineole.[14]

It can be concluded from these literature results that

cineole in tea tree oil is unlikely to present more significant allergy problems than a number of other tea tree oil constituents since, of the 11 sensitized subjects tested, only one subject responded positively to cineole.

Bioactivity

From the first reports[23] of the antimicrobial activity of tea tree oil, through to the most recent publications,[3,4,24] terpinen-4-ol has been considered the main active ingredient, with cineole having little or no activity. In experiments to assess bioactivity of mixtures of cineole and terpinen-4-ol, and possible synergism or antagonism between these compounds, minimum inhibitory concentrations (MIC) were determined by an agar dilution method.[3] As long as terpinen-4-ol concentrations were maintained at a minimum of 30%, there was no evidence of antagonism (reduced activity) due to the presence of cineole. In fact, there appeared to be a slight enhancement of activity (synergism) when the concentration of cineole was in the range of 20-30%.

Further studies were conducted on tea tree oils with terpinen-4-ol concentrations greater than 30% and high and low cineole concentrations, using *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans* as test organisms.[25] The MICs of oil which contained approximately 20% cineole were shown to be the same for each of the test organisms, as was the case for an oil which contained only 1.5% cineole, thus confirming that, within this concentration range, cineole is not an antagonist. The apparent synergistic effect previously reported[3] was not obtained in these experiments. This may be a result of varying the method to include the use of an emulsifier to ensure uniform dispersion of the oil through the agar, or it may be due to interactions with other oil components.

Consequently, the presence of cineole in tea tree oil is not at all detrimental to the general activity of the oil. In fact, the opposite may be the case. Antifungal and antihelminthic activity may be enhanced by cineole.[24]

Conclusion

There is no evidence to support the current industry misconception that tea tree oils with ultra-low levels of 1,8-cineole are superior to oils with higher levels of cineole. Standards specifying a minimum level for terpinen-4-ol and a maximum level for cineole have been interpreted wrongly to mean that terpinen-4-ol and cineole concentrations must be maximized and minimized, respectively. Cineole, in concentrations above 15%, is undesirable because of the concomitant decrease in terpinen-4-ol, the active ingredient. However, recent investigations have confirmed that cineole in concentrations up to 15% is not detrimental to the oil, as it is neither a skin irritant nor an antagonist to the activity of the oil.

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