İstanbul Journal of Pharmacy
Istanbul J Pharm2024, 54 (3): 488–495
DOI: 10.26650/IstanbulJPharm.2024.1434421

Review Article

Safety and possible risks of tea tree oil from a toxicological perspective

Sonia Sanajou[1,2], Rana Ülker Özkan[1,3], Pınar Erkekoğlu[1], Gözde Girgin[1], Terken Baydar[1]

[1]Hacettepe University, Faculty of Pharmacy, Department of Toxicology, Ankara, Türkiye
[2]İstanbul Aydın University, Faculty of Pharmacy, Department of Toxicology, İstanbul, Türkiye
[3]Turkish Medicines and Medical Devices Agency, Ankara, Türkiye

ABSTRACT

Tea tree oil (TTO) is a sophisticated essential oil extracted from the *Melaleuca alternifolia* plant. It comprises around 1,000 components with a significant presence of monoterpenes and their alcohols. Terpinen-4-ol, the monoterpene that makes up 30% to 48% of TTO essential oil, is the main factor responsible for its strong antibacterial properties. TTO has been extensively used in skin care products to treat many problems, including acne, eczema, and dandruff. TTO is included in products used by children and adults. Nevertheless, the reliability of TTO in cosmetic and dermatological or derma cosmetic formulations is contingent upon numerous influential aspects, underscoring the pivotal significance of formulation and production procedures. TTO can be taken orally, topically, or ocularly. However, it is important to exercise caution, as high levels of TTO may cause phytotoxic effects and result in negative consequences such as contact allergy, inflammation, irritation, and dermatitis. Though natural, this essential oil can be harmful if not used correctly, considering factors like the route of application, exposure dose, and poor-quality contents. This review thoroughly examines the negative consequences, considerations for safety, and regulatory factors related to the usage of TTO. The study emphasizes the importance of conducting thorough research to better understand the safe use of essential oils, especially TTO. It also calls for a full assessment of the possible negative effects on vulnerable populations. Given the increasing demand for products containing TTO, it is crucial to conduct ongoing research to improve recommendations and ensure the informed and safe use of this precious essential oil.

Keywords: Tea tree oil, Risk, Safety, Adverse effects, Essential oil

INTRODUCTION

Tea tree oil (TTO) is the essential oil obtained by distilling the leaves and terminal branchlets of the narrow-leaf tea tree *Melaleuca alternifolia*, which grows in New South Wales and Queensland in Australia. It is a pale-yellow liquid with a terpenic, coniferous, and minty–camphoraceous odor. TTO is present in many cosmetics and personal care products, including ointments, skin cleansers, and shampoos (de Groot & Schmidt 2016). TTO acts as a natural bactericide against methicillin-resistant *Staphylococcus aureus* at 0.002-2% concentrations and is also suggested to have antiviral, anti-inflammatory, and analgesic effects (Vatanen et al., 2016). The European Medicines Agency (EMA) has approved TTO to treat minor superficial wounds, insect bites, tiny boils, irritation in athlete's foot cases, and minor oral mucosa inflammation. It is mainly used against skin problems such as contact allergy, irritation, eczema, dandruff, and dermatitis (de Groot & Schmidt 2016). Figure 1 summarizes the dermatological applications, biological activities, and composition of TTO.

TTO includes about 1000 ingredients, most of which are monoterpenes and their alcohols. Terpinen-4-ol is a monoterpene and the most prevalent constituent (with a minimum of 30% and a maximum of 48%) and is responsible for most of TTO's antibacterial activity (Oliva et al. 2018). TTO also contains high amounts of γ-terpinene and 1,8-cineole (eucalyptol), both of which cause skin irritation (Zeiner, Michaela & Stingeder, 2018)Sabinene, aromadendrene, δ-cadinene, ledene (viridiflorene), limonene, globulol, and viridiflorol are also present in TTO but in lower amounts. The other high ingredients are γ-terpinene, α-terpineol, p-cymene, α-pinene, and terpinolene, with maximum levels of 13%, 8%, 8%, 6%, and 5%, respectively. The minimum and maximum amounts of these chemical components are given in Table 1.

This review primarily aims to gather and summarize the findings on the safety and regulations on the use of TTO in cosmetics and dermatological pharmaceuticals. It will also provide data on accurate and relevant information regarding the toxicity of TTO.

Corresponding Author: Sonia Sanajou **E-mail:** sanajou19@hotmail.com
Submitted: 10.02.2024 • **Revision Requested:** 18.03.2024 • **Last Revision Received:** 23.03.2024 • **Accepted:** 17.04.2024 • **Published Online:** 26.09.2024

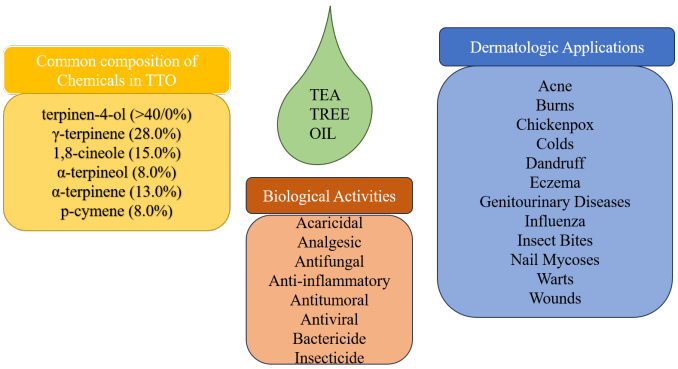
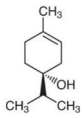
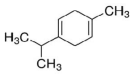
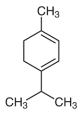
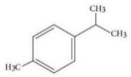
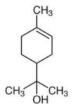
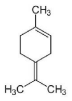


Figure 1. Summary of TTO's composition, activities, and situations where it can be applied

Table 1. *TTO's Constituents, Chemical Structures, and Percentage of Overall Content* (SCCP, 2008)

Constituent	**Content (%)**	
	Min.	**Max.**
Terpinen-4-ol 	30	48
g-terpinene 	10	28
1,8-cineole (eucalyptol) 	Trace	15
a-terpinene 	5	13
p-cymene 	0.5	8
a-terpineol 	1.5	8
α-pinene 	1	6
Terpinolene 	1.5	5

Search Strategy

The study conducts a literature search with the intent to collate, synthesize, and integrate the reports that have been published on TTO. Data have been gathered from three databases: PubMed, Web of Science, and Scopus. The searches have been restricted to papers published in English between 2015-2024, with research articles and comprehensive reviews both being chosen. The most common search terms have been chosen as "tea tree oil," safety of tea tree oil," regulations for tea tree oil," and "toxicity of tea tree oil." After searching in the databases, the exclusion criteria for the papers are articles (i) with no abstract, (ii) in languages other than English, or (iii) with no reliable data and statistics.

Safety Regarding Exposure to TTO

With regard to all the available data, TTO is considered generally safe and might help treat acne and other superficial skin infections when used topically. An earlier Scientific Committee on Consumer Products (SCCP, 2008) report calculated daily exposure to TTO for rinse-off and leave-on products. Systemic exposure levels between 1.7 and 3.33 µg/kg per day were estimated for various types of cosmetics. The SCCP report concluded that considerable systemic exposure could occur with topical application of TTO-containing products and TTO itself if used daily. The report also calculated worst-case estimations for general systemic and reproductive toxicity. However, the margin of safety (MoS) could not be calculated, as a lack of data is found regarding the bioavailability of TTO. A rate of 3% was calculated for the subcutaneous absorbance of TTO (Cross, Russell, & Roberts, 2008) . However, no data could be found on the oral bioavailability of TTO. Hence, converting between exposure routes is challenging.

Evaluating TTO Toxicity

With rising reports of TTO's therapeutic benefits, multiple TTO toxicity reviews have also been published. According to manufacturing companies, adverse effects of TTO are infrequent (less than 0.0016%) and only involve mild complaints. TTO causes numerous local adverse effects, including contact allergy (de Groot & Schmidt 2016), irritation (Zeiner et al., 2018) and dermatitis (Ambrogio et al., 2022) . However, most evidence suggests that diluting TTO can decrease these reactions.

Some components of TTO oxidize in ambient air and light, creating peroxides, epoxides, and endoperoxides, which have sensitizing properties and may cause allergic skin reactions (Ambrogio et al., 2022). These oxidation products are suggested to increase the toxicity of TTO. Although TTO is a modest skin sensitizer in susceptible individuals, oxidized TTO has stronger oxidizing effects. Manufacturers of TTO warn users against exposure to oxidized TTO (Thomas et al., 2016). According to the International Fragrance Association (IFRA), concentrated TTO is hazardous and bears the R-codes R-22 (harmful if ingested), R38 (skin irritant), and R65 (may cause lung damage if ingested), as well as the symbol Xn (harmful). These health threat indicators are also included in the safety data sheets of raw material suppliers (IFRA, 2022).

Cytotoxicity of TTO

Initially, studies were conducted to assess the cytotoxicity of TTO on cultured cells to ascertain its possible harmful effects. The toxicity of TTO was assessed over a diverse range of human cell cultures, including HeLa cervical cancer cells, MOLT-4 acute lymphoblastic leukemia cells, K562 erythromyeloblastoid leukemia cells, CTVR-1 B cells obtained from the bone marrow of a patient with acute myeloid leukemia, and fibroblast and epithelial cells. The experiments showed that TTO exhibited an inhibitory concentration 50 (IC_{50}) value for cell growth ranging from 20 to 2,700 µg/mL (Russo, Corasaniti, & Morrone, 2015). Terpinen-4-ol was shown to cause toxicity in meibomian gland epithelial cells based on dosage and exposure route (Chen, Wang & Liu, 2020) . At high concentrations, both TTO and its major ingredient terpinen-4-ol have long been known to cause cytotoxicity in human cells, including epithelial cells and fibroblasts. Moreover, TTO can exert antimicrobial activity. TTO does not directly induce cell wall alterations; however, it causes the release of autolytic enzymes associated with the cell membrane, which may induce lysis and subsequent leakage of nucleic acids across the damaged cytoplasmic membrane in bacteria (Low, Kenward & Martin, 2017).

Acute and Chronic Toxicity of TTO

TTO has an oral median lethal dose (LD_{50}) of 1,900 mg/kg in rats. According to the SCCP, undiluted TTO should not be consumed orally, as it is dangerous (Mertas et al., 2015). The LD_{50} value for γ-terpinene in orally exposed rats was found to be 5,000 mg/kg (Tabarraei, Hadi, & Mosavi, 2019). The Committee of Experts on Flavouring Substances of the Council of Europe evaluated eucalyptol as a natural flavoring content, and using a minimum lethal dose of 60 mg/kg/day with a safety factor of 300, they predicted 0.2 mg/kg/bw as tolerable daily intake (TDI) (SCCP, 2008).

No oral or dermal repeated dose toxicity studies regarding pure TTO were found in the literature. However, read-across considerations regarding the systemic toxicity of some ingredients have been performed. For terpinen-4-ol, γ-terpinene, 1,8-cineole, α-terpinene, p-cymene, α-terpineol, α-pinene, and terpinolene, the established or estimated LD_{50} and no observed adverse effect level (NOAEL) values are presented in Table 2 (European Medicines Agency, 2013).

Table 2. *Doses in Relation to TTO Constituent Toxicity and Safety* (European Medicines Agency, 2013)

TTO constituent	LD_{50} (mg/kg bw)	Animal species	Application route	NOAEL (mg/kg bw/day)	Animal species, period, toxicity
Terpinen-4-ol	1,300	rat	Oral		
	250	rabbit	dermal	400	rat, oral, 28-day study, kidney toxicity
γ-Terpinene	5,000	rat	dermal		
1,8-Cineole	430	rat	oral	300	rats and mice, subchronic toxicity study, hepatic and renal toxicity
	>2,000		dermal		
a-Terpinene	1,680	rat	oral	60	pregnant Wistar rats, oral, maternal systemic toxicity
				75	(as cumene/p-cymene) rat, oral, renal toxicity
α-Terpineol	2,900-5,170	rat	oral	500	male and female Wistar rats, oral, 28-day study
	2,000		dermal		
	2,830	mouse	oral		
	2,000		intramuscular		
α-Pinene	>2,000	rat	oral	250	weanling Osborne-Mendel male rats, oral, 28-day study, nephrotoxicity
Terpinolene	3,740	rat	oral		
	4,300	rabbit	Dermal		

TTO Toxicity Related to Exposure Routes

Essential oils enter the blood circulation in 30 seconds via mucosa and 4-12 minutes dermally. They reach internal organs and the nervous system within 20 min, resulting in systemic effects, and are excreted from the body through the kidneys (Pazyar, Yaghoobi &Kazerouni, 2013). Oral intake of the essential oil TTO lead to diarrhea, abdominal pain, rash, incoordination, and muscle weakness at relatively high doses, with these symptoms generally able to resolve within 36 hours. Oral TTO administration is not advised until more scientific investigations on its toxicity are completed (Özfenerci &Çalışkan, 2018).

Table 3 summarizes the poisoning cases in the literature. The literature does not mention cases of human death linked to TTO. A few studies have been published on accidental TTO poisoning in humans. The literature shows accidental ingestion of TTO to have varied from less than 10 mL to half a cup. Little information is found on the renal toxicity of TTO (Özfenerci &Çalışkan, 2018).

TTO is commonly administered to the skin as an essential oil. In addition, it is present in many cosmetics and personal care products, such as moisturizers, soaps, and shampoos. Therefore, dermal toxicity studies have great importance (Özfenerci &Çalışkan, 2018). After extrapolating the LD_{50} values on humans, dermally administered TTO through cosmetic products or as an essential oil can be concluded to not be assessable as harmful. Because up to 90% of TTO is a volatile liquid, it swiftly evaporates from the skin's surface. Its dermal absorption rate depends on factors such as body temperature, the integrity and age of the skin, the environment temperature and dilution rate, the amount covering the skin's surface, the chemical composition of the oil, and the application method used. TTO's lipophilic property allows it to enter the skin's surface layer; it boosts antimicrobial effects and may lead to moderate dermal toxicity (Mertas et al., 2015). However, only small amounts of the components of TTO enter the subdermal layers and into the bloodstream, with human skin not being readily able to absorb higher amounts of TTO to generate acute toxic effects (Caliskan & Karakus 2020).

In rabbits, the Draize irritation index for undiluted TTO is 5.0. This means TTO is a severe skin irritant. Human studies have presented conflicting results, such as no irritation with diluted and undiluted TTO, as well as skin irritation with undiluted TTO or cosmetic formulations containing 5% TTO. Such inconsistent results may be due to differences delivery methods, exposure routes, and exposure periods (SCCP, 2008). One Hen's Egg-Chorioallantoic Membrane Text (HET-CAM) assay found undiluted TTO and its 25% and 10% solutions in a surfactant to cause severe irritation, with TTO being a slight irritant at 5% dilution (Capasso, Abbinante & De Vernardo, 2022).

Topical administration of TTO is associated with few side effects, including irritation and allergic reactions. Irritant reactions can be reduced significantly by utilizing products with lower oil concentrations. Patch tests confirm allergic reactions

Table 3. *TTO Poisoning Case Reports in Humans*

Ingested amount	Gender and age	Clinical symptoms	Reference
½ teaspoonful	60-year-old male	a dramatic rash accompanied by leukocytosis; swollen face, hands, and feet	(Elliott, 1993)
2 teaspoons	4-year-old male	ataxia, shortly after progressed to unresponsiveness	(Morris, Donoghue, & Osterhoudt, 2003)
< 10 mL	23-mo-old male	confusion, unable to maintain balance; tripping and falling over; disorientation	(Jacobs & Hornfeldt, 1994)
< 10 mL	17-mo-old male	ataxia and drowsiness	(Del Beccaro, 1995)

to TTO can even occur at very low concentrations. Terpinen-4-ol and α-terpineol can penetrate the skin's epidermal layer and exert antibacterial, anti-inflammatory, and acaricidal effects. When testing a 20% TTO formulation in ethanol, only terpinen-4-ol (0.05% of the applied formulation) was able to completely permeate the epidermis (Thomas et al., 2016). A retrospective assessment of 41 instances of positive patch testing in Australia over 4.5 years concluded only 1.8% of the study population to be allergic to TTO (Chen et al., 2020).

Meanwhile, allergic contact dermatitis, systemic contact dermatitis, linear immunoglobulin-A disease, multiform erythema reactions, systemic hypersensitivity reactions, and idiopathic male prepubertal gynecomastia have also been observed (Mertas et al., 2015). Another study found the patch test findings of 311 volunteers to reveal an average irritancy score of 0.25. Yet another study that applied a patch test with 10% TTO to 217 people observed no irritation reaction in the volunteers, with the researchers suggesting that skin irritation could be avoided by using lower concentrations. Although many ingredients in TTO have been claimed to be able to lead to allergic reactions, the most important claim also stated that these result from oxidation products formed from outdated or badly preserved oils (Bekhof, Hunsel & Woerdenbag, 2023).

Lee et al. (2013) investigated the acute dermal toxicity of TTO using multiple dilution doses. According to their findings, skin irritation was reduced dramatically for TTO concentrations < 2.5%. They also further researched the major and minor TTO components that produce skin irritation, investigating Terpinen-4-ol, and 1,8-cineole mainly to determine whether they were the primary causes of skin irritation at a 5% concentration, TTO caused substantial skin irritation, with terpinen-4-ol comprising up to 30% of the mixture. Moreover, when examined at a concentration of 1.5%, terpinen-4-ol was determined to be non-irritating. In the Local Lymph Node Assay (LLNA), both whole TTO and its polyethylene glycol (PEG) solution (at ISO4730 quality) were found to be moderate sensitizers in mice (SCCP, 2008) .TTO is also suggested for sensitizing humans, with several patch test studies indicating an allergic contact dermatitis prevalence rate of 4.8% (European Medicines Agency, 2013) . Despite this, there is no clear data on the skin sensitization potentials of the individual constituents of TTO. Suggestions point towards the terpenoid fraction, limonene, and/or oxidative degradation products as possible culprits. Notably, oxidized TTO demonstrates three times more potent sensitization than fresh TTO. The increase in levels of p-cymene and 1,8-cineole over time may also contribute to the heightened sensitizing potency of TTO. Conversely, skin oxidative bioactivation of prohaptens to haptens is plausible. α-terpinene, a major constituent of TTO, can oxidize over time and become a hapten, potentially leading to skin sensitization (European Medicines Agency, 2013). However, further studies are necessary to determine definitively which constituent(s) of TTO are responsible for human skin sensitization.

TTO is currently being used successfully to eradicate ocular Demodex. However, an *in vitro* study showed the doses of TTO that exert demodicidal activity to be able to lead to toxic effects in human hepatic cells, cervical cells, breast epithelial cells, T cells, B cells, bone marrow cells, fibroblasts, and peripheral blood monocytes (Chen et al., 2020). A primary eye irritation study classified 1% and 5% TTO solutions as minimally irritating in rabbits. TTO concentrations less than 10% substantially reduced ocular discomfort and inflammation of the eyelids and conjunctiva (Messaoud et al., 2019) . On the other hand, TTO produces eye discomfort in certain patients when administered at high concentrations. Contact dermatitis, allergic reactions, and eye irritation are frequent consequences of TTO preparations (Ergun et al., 2020) .

Undiluted TTO was found to not cause phototoxicity in hairless mice (Infante et al., 2022). No other phototoxicity studies on TTO or its ingredients are present in the literature.

TTO's Potential for Reproductive and Developmental Toxicity

Data on the reproductive toxicity of the constituents of TTO are also limited, and the oral NOAEL values for reproductive

toxicity were found to be between 250-365 mg/kg/day. When applying α-terpinene at 30, 60, 125, and 250 mg/kg doses to female Wistar rats during their 6^{th}-15^{th} days of pregnancy, maternal toxicity was observed in both the 125 and 250 mg/kg/day dosage groups, with these two highest dosage groups showing reduced fetal body weights and increased kidney weights. Abnormal ossification of bones and minor skeletal abnormalities in fetuses were evident in the 60, 125, and 250 mg/kg dosage groups. The oral NOAEL values for embryotoxicity and fetotoxicity were suggested to be 30 mg/kg, and this value was 60 mg/kg for maternal toxicity (Cross et al., 2008; SCCP, 2008).

Genotoxicity of TTO

Testing the genotoxicity of essential oils and their components is critical for assessing their safety. The genotoxic effects of TTO and its components have been evaluated *in vitro* (Casalle & Andrade, 2020). Several mutagenicity tests in their study also examined the mutagenic potentials of TTO and its components. *Salmonella typhimurium* strains were used to test the mutagenic effects of commercially available TTOs. None of the TTO brands were found to exert a mutagenic effect on the *Salmonella* strains examined with and without metabolic activation in the Ames test. Terpinen-4-ol application also ended up with the same negative results. However, at higher doses, clear evidence of toxicity was observed in all *Salmonella* strains regarding all TTOs and terpinen-4-ol (Fletcher, Cassella & Cassella, 2005). Therefore, terpinen-4-ol was suggested as being the main constituent responsible for the significant antibacterial activity of TTO.

A genotoxicity study (Gomes-Carneiro, Felzenszwalb & Paumgartten, 1998) using *Salmonella typhimurium* strains with and without S9-mix reported no effect for TTO applications ranging from 100-1,500 µg/plate, Although TTO and most of its constituents are non-mutagenic, α-terpineol was found to cause a slight mutagenic effect related to dosage (0-2,500 µg/plate) in *Salmonella typhimurium* strain TA102 with or without metabolic activation. The other bacterial mutagenicity test strains in their study showed no mutagenic effects.

Moreover, several constituents of TTO were found to exert no mutagenic activity in various mammalian cells (SCCP, 2008). For example, Australian TTO (Batch ATTIA/0501) was tested to induce micronuclei in mouse bone marrow. Application doses were selected according to the preliminary study on mice conducted at oral doses between 500-2,000 mg/kg. All animals in the highest dose group showed wobbly gait, prostration, and labored breathing between 30 min-5 h after dosing. Polychromatic erythrocytes prepared from the bone marrow of each animal were counted for the incidence of micronucleated polychromatic erythrocytes. As a result, SCCP's study suggested Australian TTO to be non-clastogenic regarding the mouse micronucleus test.

No carcinogenicity studies have been performed with TTO or its constituents in the literature.

CONCLUSION

Many essential oils do not possess harmful effects and can be used safely via dermal application. However, concerns exist that some of these oils can be inhaled after dermal absorption, and inhalation may lead to systemic toxicity. Current scientific publications are limited, with most data having been obtained from observational *in vitro* studies. Therefore, the mechanisms underlying the toxicity of essential oils are not well documented. The past decade has seen increased interest in non-traditional and non-prescription natural medicines. Also, new approaches need to be found for treating skin diseases. When used and stored correctly (i.e., well-sealed and away from light and heat), TTO poses no danger to human health. Therefore, after reviewing the literature, this study can suggest TTO to be safe for treating dermatologic illnesses.

The stability of TTO in cosmetics and personal care products is affected by several factors. Undiluted TTO should not be used, as it clearly can cause skin reactions. Good formulation design and production techniques are critical. Moreover, users should store prepared products properly. They should be kept away from direct sunlight and avoid excessive exposure to heat and air. Antioxidants can be added to TTO formulations to prevent terpene oxidation, which causes skin sensitization. For example, one study collected storage stability data on different formulated items and monitored product stability using TTO's p-cymene content (European Medicines Agency 2013). The p-cymene content generally increased with storage duration but remained below the International Organization for Standards' upper limits.

Concluding whether or not herbal remedies pose a danger to human health is usually a complicated issue, as they are composed of various components. The effects and toxicities of herbal remedies arise as a combined effect of different chemical compounds with different characteristics. In the case of TTO, the components can make up anywhere from 1% to 48% of the total oil. Meanwhile, with their varying structures and physicochemical properties, these constituents have different kinetics and oxidation rates, thus adding another challenging and important issue regarding the further toxicological evaluation of TTO.

In conclusion, this study suggests that fresh products containing TTO are able to treat certain skin conditions at proper concentrations. As oxidation of certain constituents occurs over time, TTO should not be used after a certain date. Meanwhile, oral administration should be avoided. More in vitro and in vivo studies are needed to reveal the full safety profile of TTO and its constituents.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- T.B., G.G.; Data Acquisition- R.Ü.Ö., S.S.; Data Analysis/Interpretation- G.G., P.E., R.Ü.Ö., S.S.; Drafting Manuscript- G.G., P.E., R.Ü.Ö., S.S.; Critical Revision of Manuscript- T.B., S.S., P.E.; Final Approval and Accountability- S.S., R.Ü.Ö., P.E., G.G., T.B.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared no financial support.

ORCID IDs of the authors

Sonia Sanajou	0000-0002-6751-5266
Rana Ülker Özkan	0000-0001-6812-581X
Pınar Erkekoğlu	0000-0003-4713-7672
Gözde Girgin	0000-0002-7051-0490
Terken Baydar	0000-0002-5497-9600

REFERENCES

Ambrogio, F., Foti, C., Cazzato, G., Mortato, E., Mazzoccoli, S., De Caro, A. P., ... Romita, P. (2022). Spreading allergic contact dermatitis to tea tree oil in an over-the-counter product applied on a wart. *Medicina (Kaunas, Lithuania), 58*(5), 561. https://doi.org/10.3390/medicina58050561

Bekhof, A. M. W., van Hunsel, F. P. A. M., van de Koppel, S., & Woerdenbag, H. J. (2023). Safety assessment and adverse drug reaction reporting of tea tree oil (Melaleuca aetheroleum). *Phytotherapy Research, 37*(4), 1309–1318. https://doi.org/10.1002/ptr.7687

Caliskan, U. K., & Karakus M. M. (2020). Essential Oils as Skin Permeation Boosters and Their Predicted Effect Mechanisms. Journal of Dermatology and Skin Science 2(3).

Capasso, L., Abbinante, G., Coppola, A., Salerno, G., & De Bernardo, M. (2022). Recent evidence of tea tree oil effectiveness in blepharitis treatment. *BioMed Research International, 2022*, 9204251. https://doi.org/10.1155/2022/9204251

Casalle, N., & de Andrade C.R. (2020). Cytotoxic and mutagenic capacity of TTO and terpinen-4-ol in oral squamous cell carcinoma. *BioRxiv*. https://doi.org/10.1101/2020.01.03.893735.

Chen, D., Wang, J., Sullivan, D. A., Kam, W. R., & Liu, Y. (2020). Effects of terpinen-4-ol on meibomian gland epithelial cells *in vitro*. Cornea, 39(12), 1541–1546. https://doi.org/10.1097/ICO.0000000000002506

Cross, S. E., Russell, M., Southwell, I., & Roberts, M. S. (2008). Human skin penetration of the major components of Australian tea tree oil applied in its pure form and as a 20 solution *in vitro. European Journal of Pharmaceutics and Biopharmaceutics, 69*(1), 214–222. https://doi.org/10.1016/j.ejpb.2007.10.002

de Groot, A. C., & Schmidt, E. (2016). Tea tree oil: contact allergy and chemical composition. *Contact Dermatitis, 75*(3), 129–143. https://doi.org/10.1111/cod.12591

Del Beccaro M. A. (1995). Melaleuca oil poisoning in a 17-month-old. *Veterinary and Human Toxicology, 37*(6), 557–558.

Elliott C. (1993). Tea tree oil poisoning. *The Medical Journal of Australia, 159*(11-12), 830–831. https://doi.org/10.5694/j.1326-5377.1993.tb141370.x

Ergun, S. B., Saribas, G. S., Yarayici, S., Elmazoglu, Z., Cardak, A., Ozogul, C., ... Evren Kemer, O. (2020). Comparison of efficacy and safety of two tea tree oil-based formulations in patients with chronic blepharitis: a double-blinded randomized clinical trial. *Ocular Immunology and Inflammation, 28*(6), 888–897. https://doi.org/10.1080/09273948.2019.1644349

European Medicines Agency (2013). Assessment Report on Melaleuca Alternifolia (Maiden and Betch) Cheel, M. Linariifolia Smith, M. Dissitiflora F. Mueller and/or Other Species of Melaleuca, Aetheroleum. *European Medicines Agency* 44(July):73.

Fletcher, J. P., Cassella J. P., Hughes D., & Cassella S. (2005). An Evaluation of the mutagenic potential of commercially available tea tree oil in the United Kingdom. *International Journal of Aromatherapy, 15*(2):81–86. doi: 10.1016/j.ijat.2005.03.004.

Gomes-Carneiro, M. R., Felzenszwalb, I., & Paumgartten, F. J. (1998). Mutagenicity testing (+/-)-camphor, 1,8-cineole, citral, citronellal, (-)-menthol and terpineol with the Salmonella/microsome assay. *Mutation Research, 416*(1-2), 129–136. https://doi.org/10.1016/s1383-5718(98)00077-1

IFRA (2022). The Complete IFRA Standards. https://ifrafragrance.org/docs/default-source/ifra-code-of-practice-and-standards/ifra-standards—50th-amendment/standards-compiled.pdf

Infante, V. H. P., Maia Campos, P. M. B. G., Gaspar, L. R., Darvin, M. E., Schleusener, J., Rangel, K. C., ... Lademann, J. (2022). Safety and efficacy of combined essential oils for the skin barrier properties: *In vitro, ex vivo* and clinical studies. *International Journal of Cosmetic Science, 44*(1), 118–130. https://doi.org/10.1111/ics.12761

Jacobs, M. R., & Hornfeldt, C. S. (1994). Melaleuca oil poisoning. Journal of toxicology. *Clinical Toxicology, 32*(4), 461–464. https://doi.org/10.3109/15563659409011050

Lee C.J., Chen L.W., Chen L.G., Chang T.L., Huang C.W., Huang M.C., & Wang C.C. (2013). Correlations of the components of tea tree oil with its antibacterial effects and skin irritation. *Journal of Food and Drug Analysis, 21* (2), 169-176. https://doi.org/10.1016/j.jfda.2013.05.007

Low, W. L., Kenward, K., Britland, S. T., Amin, M. C., & Martin, C. (2017). Essential oils and metal ions as alternative antimicrobial agents: a focus on tea tree oil and silver. *International Wound Journal, 14*(2), 369–384. https://doi.org/10.1111/iwj.12611

Mertas, A., Garbusińska, A., Szliszka, E., Jureczko, A., Kowalska, M., & Król, W. (2015). The influence of tea tree oil (Melaleuca alternifolia) on fluconazole activity against fluconazole-resistant Candida albicans strains. *BioMed Research International, 2015*, 590470. https://doi.org/10.1155/2015/590470

Messaoud, R., El Fekih, L., Mahmoud, A., Ben Amor, H., Bannour, R., Doan, S., & Khairallah, M. (2019). Improvement in ocular symptoms and signs in patients with Demodex anterior blepharitis using a novel terpinen-4-ol (2.5%) and hyaluronic acid (0.2%) cleansing wipe. *Clinical Ophthalmology, 13*, 1043–1054. https://doi.org/10.2147/OPTH.S198585

Morris, M. C., Donoghue, A., Markowitz, J. A., & Osterhoudt, K. C. (2003). Ingestion of tea tree oil (Melaleuca oil) by a 4-year-old boy. *Pediatric Emergency Care, 19*(3), 169–171. https://doi.org/10.1097/01.pec.0000081241.98249.7b

Oliva, A., Costantini, S., De Angelis, M., Garzoli, S., Božović, M., Mascellino, M. T., Vullo, V., & Ragno, R. (2018). High potency of *Melaleuca alternifolia* essential oil against multi-drug

resistant gram-negative bacteria and methicillin-resistant *Staphylococcus aureus. Molecules (Basel, Switzerland), 23*(10), 2584. https://doi.org/10.3390/molecules23102584

Özfenerci, M. & Ufuk Koca Çalışkan U.K. (2018). Tea Tree Oil and Its Use in Aromatherapy. *Current Perspective on Medicinals and Aromatic Plants*. 90–102.

Pazyar, N., Yaghoobi, R., Bagherani, N., & Kazerouni, A. (2013). A review of applications of tea tree oil in dermatology. *International Journal of Dermatology, 52*(7), 784–790. https://doi.org/10.1111/j.1365-4632.2012.05654.x

Russo, R., Corasaniti, M. T., Bagetta, G., & Morrone, L. A. (2015). Exploitation of cytotoxicity of some essential oils for translation in cancer therapy. *Evidence-based Complementary and Alternative Medicine: eCAM, 2015*, 397821. https://doi.org/10.1155/2015/397821

SCCP. 2008. *Scientific Committee on Consumer Products - OPINION ON Tea Tree Oil*. https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_160.pdf

Tabarraei H., Hassan J., & Mosavi S.S. (2019). Determination of LD50 of some essential oils and histopathological changes in short-term exposure to one of them in rainbow trout *(Oncorhynchus mykiss). Toxicology Research and Application,3*. doi:10.1177/2397847318820719

Thomas, J., Carson, C. F., Peterson, G. M.,Walton, S. F., Hammer, K. A., Naunton, ... Baby, K. E. (2016). Therapeutic potential of tea tree oil for scabies. *The American Journal of Tropical Medicine and Hygiene, 94*(2), 258–266. https://doi.org/10.4269/ajtmh.14-0515

Vatanen, T., Kostic, A. D., d'Hennezel, E., Siljander, H., Franzosa, E. A., Yassour, M., ... Xavier, R. J. (2016). Variation in microbiome LPS immunogenicity contributes to autoimmunity in humans. *Cell, 165*(4), 842–853. https://doi.org/10.1016/j.cell.2016.04.007

Zeiner, M., Cindrić I.J., Kandler W., & Stingeder G. (2018). Trace determination of skin-irritating metals in tea tree oil by GFAAS. *Microchemical Journal, 136*:101–5. doi: 10.1016/j.microc.2016.12.016.

How cite this article

Sanajou, S., Ülker Özkan, R., Erkekoğlu, P., Girgin, G., & Baydar, T. (2024). Safety and possible risks of tea tree oil from a toxicological perspective. *İstanbul Journal of Pharmacy, 54*(3): 488–495. DOI: 10.26650/IstanbulJPharm.2024.1434421