The allergic potential and xenobiotic metabolism of anethole in toothpaste: A scoping review

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Abstract

Background: Ingredients that have a role as fragrance and flavoring in toothpaste have the potential to cause allergies and irritation to the body, especially to the mucous tissue in the mouth. Diseases of the oral mucosa are very common: recurrent aphthous stomatitis (recurrent oral ulceration) affects 20% of the population. Therefore, allergenic substances such as anethole toothpaste on the patient's oral symptoms (stomatitis, glossitis, gingivitis, buccal mucositis, burning, pain, and possibly burning mouth syndrome and recurrent aphthous ulcers) are unclear and should be further investigated.
Purpose: To investigate and provide further explanation of our body's xenobiotic metabolic reactions to anethole.
Method: We collected and analyzed several research journal articles related to the effects of anethole compounds.
Results: The majority of articles indicated the role of the tiny anethole as an allergen. The dose of anethole which is generally contained in toothpaste normally is really low so that within an average of 72 hours it is likely to have been completely eliminated from the body's system.
Conclusion: Claims of anethole compound C10H12O as a cause of irritation or inflammation are inaccurate and considered too explicit as the main factor causing allergies.

Keywords: Allergen; Anethole; Metabolism; Toothpaste; Xenobiotic.

INTRODUCTION

Allergic reactions to toothpaste are infrequent. It clearly cannot be underestimated because it is still highly risky although rarely lethal. However, if not treated properly can lead to anaphylaxis which is life threatening. Research conducted by Turner published in 2015, hospital admissions from all-cause anaphylaxis increased by 615% over the time period studied (from 1992 to 2012), but fatality rates remained stable annually at 0.047 cases per 100.000 population (Turner, Arasi, Ballmer-Weber, Baseggio Conrado, Deschildre, & Gerdts, 2022). Allergic reactions may also manifest into oral mucosal disease even though it has not been widely investigated. Yet, oral mucosal disease affects 20% of the population (Wray, Rees, Gibson, & Forsyth, A. (2020). These targeted disease are recurrent aphthous stomatitis (RAS), orofacial granulomatosis (OFG), oral lichen planus (OLP), angioedema (AE) and erythema multiforme (EM). Patients who suffer from recurrent aphthous stomatitis (RAS) and orofacial granulomatosis (OFG) or cheilitis granulomatosa (CG) are agitated to show contact urticaria reactions to perfumes and flavorings (Denaxa & Arkwright, 2020).

Flavorings agents like anethole in toothpaste are aimed to give the ‘fresh clean taste’ and conceal the bitter taste of pyrophosphates in tartar-control toothpaste (Levine, 2020). And these are the commonest ingredients that cause allergies. According to Walgreen databases, 95% toothpastes have proven to contain flavors or fragrances. The most general flavorings that are frequently responsible for toothpaste allergies are cinnamal, spearmint, peppermint, carvone, and anethole (Francalanci, Sertoli, Giorgini, Pigatto, Santucci, & Valsecchi, R. 2020). In this article, we will delve further into the allergic reaction caused by anethole (1-methoxy-4-propenyl-benzene, isoestragole).

Indeed, anethole has always been incorporated into pharmaceuticals industries as a flavor agent. Anethole has the ability to mask unpleasant odors hence it is formulated into children's toothpaste. Children's toothpaste should encourage flavor design and contain less fluoride than adult's toothpaste to prevent developing the risk of fluorosis in permanent teeth (Stovell, Newton, & Lynch,

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2023). Thus, this review will examine and compare the effects of anethole and how our body metabolism will react to it. This review article aims to investigate and provide further explanation of our body's xenobiotic metabolic reactions to anethole (Guengerich, & Isin, 2024).

RESEARCH METHOD

This study employed a literature review method to examine the potential risks associated with anethole, a fragrance and flavor compound commonly found in toothpaste, and its effects on human body systems. Relevant scientific literature was systematically collected from reputable academic databases, including peer-reviewed journals, review articles, and experimental studies that discuss anethole's chemical properties, biological activities, and toxicological profiles. The selection of sources focused on studies published in recognized scientific journals to ensure the credibility and reliability of the data analyzed.

The literature selection process involved screening articles based on their relevance to anethole exposure, particularly in the context of oral care products such as toothpaste. Studies addressing the metabolism, absorption, and physiological effects of anethole on various body systems such as the digestive, endocrine, and nervous systems were prioritized. Both in vitro and in vivo studies, as well as epidemiological findings, were included to provide a comprehensive understanding of anethole's potential health impacts.

After the collection process, the selected literature was analyzed qualitatively by comparing findings across different studies to identify consistent patterns, potential risks, and knowledge gaps. The results of these studies were synthesized to evaluate the overall implications of anethole exposure from toothpaste use on human health. This approach allowed for a critical assessment of existing scientific evidence and supported the discussion on the safety and risks of fragrance and flavor compounds in oral hygiene products.

RESEARCH RESULTS

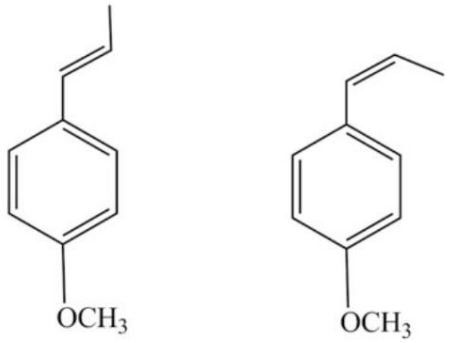


Figure 1. Properties of Anethole

Anethole is produced by rectifying crude sulfate turpentine and/or synthesizing it organically utilizing methylchavicol, anisole, and propionic anhydride as starting materials. The trans- or E isomer is the more prevalent isomer and the one that is most frequently used. About 90 % of natural anethole is trans-isomer. Given that it is 13 times sweeter than sugar, it is undoubtedly sweet. Compared to natural compounds, synthetic trans-anethole is impurified with higher amounts of cis-isomer. Based on that statement, it is no surprise Trans-anethole is usually used as a masking agent in cosmetics, soaps, and oral hygiene products because it can hide unpleasant aromas, particularly acidic, rancid, and sulfurous malodors.

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Figure 2. Cheilitis

Cheilitis is understood as referring to an inflammatory process that manifests on the lips, either the cutaneous section or the contiguous semi-mucosal area called the vermilion (the lips in the common use of the term), and the mucosal section of the internal lip. Types of cheilitis are usually recognizable by their typical clinical features (e.g., angular, exfoliative, and herpetic), although some do not have a specific picture, thus need advanced diagnostic management to reach a correct diagnosis. Orofacial granulomatosis (OFG) or cheilitis granulomatosa (CG) is a rare disease that is potentially found in patients who are sensitive to flavorings.



Figure 3. Oral Lichen Planus

Stomatitis manifests in swelling and redness of the oral mucosa or discrete, painful ulcers (single or multiple). Less commonly, whitish lesions form. Rarely, the mouth appears normal despite significant symptoms (burning mouth syndrome). Recurrent aphthous stomatitis (RAS) means the lesions happen repeatedly and usually as a response to bacterial infections, allergies, vitamin and microelement deficiencies, hormonal imbalance, mechanical injuries, and stress.



Figure 4. Erythema Multiforme (EM)

Angioedema is a non-fatal edema localized in the deeper layers of the skin and mucosa and lasting for

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several days. Considered as fatal, if it involves the larynx and other digestive organs. Erythema multiforme is red spots (macules or papules), or ridges (wheals), and sometimes blisters appear on the tops of the hands and forearms or other parts of the body, often times associated with cheilitis or vice versa.

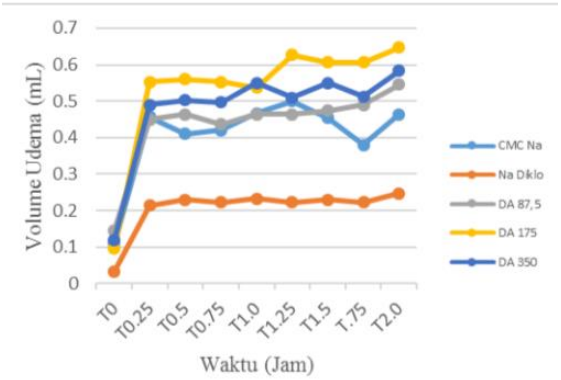


Figure 5. Graph of Average Udema Volume of Fennel Leaf Ethanol Extract, (Diclo Na)

DISCUSSION

Experimental studies in mice and rats show that anethole is absorbed completely but at a slow rate after oral intake. The main metabolic pathways involve O-demethylation, oxidation of the C3 side chain , and conjugation with glucuronic acid, glycine, sulfate, and glutathione. The main metabolites of anethole are 4-methoxy-hippuric acid, 4-methoxy-benzoic acid, 4-hydroxypropenylbenzene, 2-hydroxy-1-methylthio-1-(4'-methoxyphenyl)-propane, 4-methoxy acetophenone derivatives, cinnamic alcohol, and cinnamic acid. Eradication of anethole occurs within 48-72 hours, and the main routes are renal, pulmonary, and fecal excretion. Metabolism and excretion of anethole are dose-dependent in humans (de Groot, 2017). Low doses of anethole are mainly metabolized via O-demethylation and eliminated through exhalation as CO2. With increasing doses, anethole metabolism involves side chain oxidation and epoxidation, and renal excretion predominates. In humans, anethole is mainly metabolized to anisic acid, p-hydroxybenzoic acid, and 4-methoxy-hypuric acid. Anethole metabolites are eliminated within 8 hours after anethole administration, and the main routes include renal excretion (54-69%) and respiratory (13-17%) (Lugović-Mihić, Blagec, Japundžić, Skroza, Delaš Adžajić, & Mravak-Stipetić, 2020).

The main symptoms of allergic reactions to toothpastes are eczema of the lips (cheilitis), with or without eczema around the lips, and intraoral inflammation such as glossitis, gingivitis, and stomatitis (van Amerongen, de Groot, Volkering, & Schuttelaar, 2020). Angioedema, ulceration, or lichenoid reactions are just a few of the many different ways that allergic reactions to these antigens may present themselves. However, the role of toothpaste allergy in the development of oral mucosal illness has not received enough attention. This paper will further explain various manifestations of toothpaste allergy (Bontemps, Gaultier, Anagnostou, Ejeil, & Dridi, 2021). Glossitis refers to inflammation of the tongue; almost most causes are benign or idiopathic, glossitis can be the presenting symptom of more serious systemic conditions. It is highly likely that excess use of dental care products, such as toothpaste, can be the cause of glossitis even though there are also other prominent causes such as vitamin B12 deficiency and fungal exposure (Chiang, Chang, Wang, Wu, Wu, & Sun, 2019).

Gingivitis is considered to be the most frequent disease to appear among all periodontal diseases. Drug-induced gingivitis processes the ability of the metabolites of these drugs to induce the proliferation of fibroblasts. An imbalance between the synthesis and the degradation of the extracellular matrix leads to the accumulation of immature proteins in the extracellular matrix, particularly collagen. This results in gingivitis (Maurer, Magerl, Ansotegui, Aygören-Pürsün, Betschel, Bork, & Craig, 2018).

Table below consists of all research, studies,

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case reports on the effects of anethole compounds on toothpaste. After sorting various research journals, articles, studies, and case reports, we decided to include these four case reports and three research studies to review. Based on the four case reports listed on the table. All four of them (Marin-Cabanas, Bouret, Leiva-Salinas, Frances, & Silvestre, 2025). indicate that anethole compound is indeed responsible for causing allergic reactions. A 15-year-old girl presented with a 1.5-year history of a pruritic perioral rash (Aschenbeck & Hylwa, 2017). It is known that she had previously consumed oral antibiotics which improved her symptoms, but the rash recurred when the course was completed. It is later found out that permanent results came after she stopped using her anethole-containing toothpaste. But, many variables from this case is remained to be uncleared like such as the frequency of brushing the teeth in a day and the dose of toothbrushes that are routinely used by the patient, therefore in this case, extended contact time with the external, perioral skin from possibly unkempt brushing likely contributed to this patient's symptom (Słowianek, Majak, Leszczyńska, Smolińska, Mańkowska, Buczyłko, & Wagner, 2020).

Patch testing were implemented during both of those cases and both results show that anthole is capable of triggering cheilitis and possibly teeth hypersensitivity (Horst, Leysen, Mellaerts, Lambert, & Aerts, 2017). Using rat models for subjects, they inisists that drug-induced Anethole may have a potent inhibitory effect on periodontitis (Moradi, Abbasipour, Zaringhalam, Maleki, Ziaee, Khodadoustan, & Janahmadi, 2024). Unfortunately, it should be noted that there were no human trials conducted on their research. While Moradi and his team believe that antehole may be capable of slowing down the inflammatory process, on the other hand indicates the opposite. As a matter of fact the extract of fennel leaves 87.5mg which contains trans-anethole as much as 31.49% showed no anti-inflammatory response activity was tested using animal leg edema tests A method, using a tool to measure the volume of the legs in test animals, namely the plastimograph filled with mercury (Lugović-Mihić, Pilipović, Crnarić, Šitum, & Duvančić, 2018).

Graph of Average Udema Volume of Fennel Leaf Ethanol Extract, (Diclo Na): Diclofenac Sodium, (DA 87.5): Fennel leaves 87.5 mg/KgBW, (DA 175): Fennel leaves 175 mg/KgBB and (DA 350): Fennel leaves 350 mg / KgBB. The figure shows that the negative control group and the ethanol extract group of fennel leaves have almost the same volume of edema. This means that the ethanol extract of fennel leaves did not show anti-inflammatory activity at a dose variation of 87.5; 175 and 350 mg/kgBw. Slowaniek and his team strengthen this by claiming they found the presence of Bet v 1 and profilin analog which are known to be reactive to IgE antibodies. Therefore, we conclude that anethole compounds found in toothpaste can indeed potentially act as allergen (Abdul & Qonitah, 2021).

CONCLUSION

The human xenobiotic metabolism process will begin immediately and eliminate anethole substance within 48-72 hours, through renal, pulmonary, and fecal excretion. However, that does not erase the potential ability of anthole to act as allergen. Anethole is definitely not the main cause of inflammation in the oral area. Therefore, a claim of anetholes in toothpaste as the main perpetrator for causing cheilitis, glossitis, gingivitis, stomatitis, and erythema multiforme is inaccurate.

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