CLINICALLY RELEVANT ALLERGENS AND SOCIODEMOGRAPHIC CHARACTERISTICS IN PATIENTS WITH ALLERGIC CONTACT CHEILITIS, A CROSS-SECTIONAL STUDY

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2025

การศึกษาแบบตัดขวางถึงอาการทางคลินิกที่สัมพันธ์กับสารก่อภูมิแพ้และลักษณะทางข้อมูลสังคมประชากรผู้ป่วยผื่นแพ้สัมผัสบริเวณริมฝีปาก

ชนากานต์ คณิสสรมงคล

ปริญญานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตร
วิทยาศาสตรมหาบัณฑิต สาขาวิชาตจวิทยา
คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ
ปีการศึกษา 2568

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A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of MASTER OF SCIENCE

(Dermatology)

Faculty of Medicine, Srinakharinwirot University

2025

THE THESIS TITLED

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BY

CHANAKARN KNITSORNMONGKOL

HAS BEEN APPROVED BY THE GRADUATE SCHOOL IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE MASTER OF SCIENCE
IN DERMATOLOGY AT SRINAKHARINWIROT UNIVERSITY

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Author	CHANAKARN KNITSORNMONGKOL
Degree	MASTER OF SCIENCE
Academic Year	2025
Thesis Advisor	Chotinij Lertphanichkul , M.D.

Background: Allergic contact cheilitis (ACC) is a subtype of allergic contact dermatitis affecting the lips, often caused by allergens in daily-use products. Accurate diagnosis through patch testing is essential for effective management. **Objective**: To identify common allergens and their clinical relevance in patients with ACC and assess the impact of allergen avoidance on quality of life. **Methods**: This prospective study included patients with cheilitis who referred for patch testing between January 2024 and December 2024 at the Srinakharinwirot (SWU) Skin Center, Bangkok, Thailand. They were all patch tested with the SWU Baseline Series, our dental and cheilitis series, our preservative and vehicle series, and patient's personal products. Patch test readings were performed on Days 2, 3, and 7. A diagnosis of ACC was established based on the clinical presentation of an eczematous lip lesions and at least one relevant positive patch test result. Follow-up evaluations were performed on Days 14 and 49 to assess clinical improvement, patients' quality of life using the Dermatology Life Quality Index (DLQI), and adverse events (i.e., erythema, dyspigmentation, flaring of dermatitis, and pruritus). **Results**: A total of 80 patients were included with 78 patients diagnosed with ACC. The majority were female (92.30%), with a mean age of 30.11 years. The average symptom duration was 20.27 months, with 83.34% experienced symptoms lasting over three months. Allergic rhinitis was the most frequent comorbidity. The most frequent clinically relevant allergens were hydroperoxides of linalool (SPIN 5585.64.62), gallate mix (SPIN 2096.67), sodium benzoate (SPIN 1665.64), propylene glycol (SPIN 1601.03), and *Myroxylon pereirae* (SPIN 1270.77). Common sources were lip products and toothpaste. Personal product testing showed 14.92% positives (lip products 8.64%, toothpaste 4.18%). Mean DLQI significantly improved from 10.10 at baseline to 2.42 by Day 49 following allergen avoidance. Patch testing was well tolerated, with only transient erythema and mild post-inflammatory hyperpigmentation. Dermatitis flare-ups were infrequent and resolved with allergen avoidance or minimal intervention. Pruritus peaked in the early post-test period and near resolved by Day 49. **Conclusion**: Gallate mix, hydroperoxides of linalool, and sodium benzoate are top three allergens in ACC. Allergen avoidance significantly improves patients' quality of life. highlighting the importance of individualized allergen identification in ACC management.

Keyword : Allergic contact cheilitis, Allergic contact dermatitis, Contact allergy, Contact dermatitis, Lip dermatitis, Thailand

ACKNOWLEDGEMENTS

This thesis has been successfully completed thanks to the kindness and generous support of many individuals.

I would like to express my deepest gratitude to my thesis advisor, Dr. Chotinij Lertphanichkul, M.D., for her invaluable guidance, thoughtful advice, and constant encouragement throughout every stage of this research. Her dedication and support have been essential in helping me complete this work to the best of my ability.

I would also like to sincerely thank Dr. Pailin Puangpet, M.D., Chair of the Oral Examination Committee, for her insightful feedback and meaningful suggestions, which greatly contributed to the quality and clarity of this study. My heartfelt thanks also go to Assistant Professor Dr. Saranya Khunkhet, M.D., who served as a committee member and provided expert advice.

Special thanks are extended to Professor Dr. Montree Udompataikul, M.D., Associate Professor Dr. Salinee Rojanahirunyasakul, M.D., Assistant Professor Dr. Saranya Khunkhet, M.D., and Dr. Nunticha Komnamool, M.D., who served on the research proposal review committee. Their valuable comments and guidance helped shape the direction of this study and ensured its academic integrity.

I gratefully acknowledge the financial support from the Medical Center's internal research fund for the fiscal year 2023, which enabled the smooth and successful completion of this research.

I also wish to express my sincere appreciation to all the physicians and staff members at the Dermatology Center, Faculty of Medicine, Srinakharinwirot University, for their kind assistance and continuous encouragement.

Lastly, I sincerely hope that this research will be of benefit, even in a small way, to those who are interested in further studies on this topic.

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CHAPTER 1

Introduction

Background and significance

Cheilitis, or inflammation of the lips, is one of the common dermatological conditions that affects individuals of all ages and backgrounds. The clinical presentation of cheilitis varies depending on the underlying cause but typically includes erythema, swelling, dryness, itching, burning, fissuring, and flaking of the lips. Cheilitis may be acute or chronic course and can affect the vermilion border, the perioral area, less often, the oral mucosa.

While cheilitis can be caused by a variety of factors, including infection, trauma, chronic sun exposure, nutritional deficiencies, and systemic diseases, contact hypersensitivity is also recognized as a significant contributor to the development and exacerbation of cheilitis. [(1)]

Contact hypersensitivity is a type of delayed hypersensitivity reaction that occurs when the skin comes into contact with an allergen, leading to an immune response and subsequent inflammation.

The pathogenesis of contact hypersensitivity in cheilitis involves a complex interplay between environmental factors and immune responses. When an allergen comes into contact with the skin, it can penetrate the stratum corneum and activate antigen-presenting cells, such as Langerhans cells, which then migrate to the regional lymph nodes to activate T cells. The activated T cells subsequently migrate back to the site of allergen exposure and release pro-inflammatory cytokines, leading to local inflammation and tissue damage. [(2)]

In the case of cheilitis, contact with a variety of allergens such as lipsticks, lip balms, and dental products can cause a localized reaction resulting in cheilitis. [(1)]

Patch testing is the gold standard for diagnosing contact hypersensitivity. It involves the application of a panel of potential allergens to the skin, typically on the back, and monitoring for an immune response over a period of several days. Patch testing is

useful in identifying the specific allergen causing the reaction and guiding subsequent management strategies. [3]

Despite the known association between cheilitis and contact hypersensitivity, there is limited information regarding the allergen frequencies, relevance, relevant allergic sources and patient characteristic of this condition in Thai population. A better understanding of the above-mentioned information will provide an insightful data for dermatologists in many ways such as selecting suitable and relevant allergen series for patch testing, knowing type of patient's own products needed to be tested. Learning patient characteristics helps dermatologists aware of this condition in such patients. These will ultimately result in early and effective diagnosis, prompt patient management in terms of symptomatic relief and prevention of recurrence.

Therefore, the aim of this study is to determine the clinically relevant allergens in Thai patients with allergic contact cheilitis and to identify the associated risk factors, including demographic, clinical, and environmental factors. Additionally, this study will assess the impact of allergic contact cheilitis on the quality of life of affected individuals.

Objectives

Primary objective

To determine the clinically relevant allergens in patients with allergic contact cheilitis.

Secondary objectives

1. To determine the patient characteristics and associated factors in a patient with allergic contact cheilitis.

2. To assess the impact of allergic contact cheilitis on the patient's quality of life.

3. To compare patient's quality of life pre- and post- allergen avoidance in the patients with definitive diagnosis of allergic contact cheilitis.

Research Question

Primary research question:

What are the most relevant allergens causing allergic contact cheilitis?

Secondary research question:

1. Are there any demographic or associated factors that are related to an increased risk of developing allergic contact dermatitis in patients with cheilitis?

2. Does allergic contact cheilitis impact the patient's quality of life?

3. Is there any improvement on patient's quality of life in a patient pre- and post- allergen avoidance in the patients with definitive diagnosis of allergic contact cheilitis?

Hypothesis

Primary Hypothesis:

Clinically relevant allergens of allergic contact cheilitis in the Thai population are similar to general populations.

Secondary Hypothesis:

1. Female, and atopic dermatitis is related to an increased risk of developing allergic contact dermatitis in patients with cheilitis.

2. Allergic contact cheilitis has a moderate to very large impact on the patient's quality of life.

3. After allergen avoidance, the quality of life in a patient with allergic contact cheilitis will be improved.

Conceptual of Research

The study is a cross-sectional descriptive study to determine the clinically relevant allergens in Thai patients with allergic contact cheilitis and to identify the associated risk factors including demographic, clinical, and environmental factors. Additionally, this study will assess the impact of allergic contact cheilitis on the quality of life of affected individuals.

All patients with an unidentified cause of cheilitis who visit the Dermatology Clinic, Department of Dermatology, Srinakharinwirot University (SWU) from January to December 2024 will be enrolled in this study. All participants will be patch tested to SWU Baseline Series (Modified European Baseline Series), SWU Vehicles, Preservative and other supplemental allergen series, SWU Dental and Cheilitis Series, and up to 10 patients' own products. Positive and relevant reactions will be recorded. The duration of the study is 49 days (Follow up on days 0, 2, 3, 7, 14, 49). Lasty, the quality of life of the participant will be assessed by the dermatologic life quality of life index (DLQI) questionnaire.

Expected Benefits

1. With better understanding of the allergen frequencies, relevance, and relevant allergic sources of patients with allergic contact cheilitis, dermatologists will be able to select appropriate patch testing series for an accurate diagnosis.

2. With better understanding of patient characteristics in patients with allergic contact cheilitis, dermatologists will have an awareness of this condition in patients with such characteristics.

3. Identification of new relevant allergic sources including new relevant allergens and/or specific ingredients which commonly present in oral care products in Thai market. This information could help manufacturers in ingredient selection and moreover could help in developing a regulation for product labeling.

4. Increased awareness among healthcare providers of the potential for oral care products such as mouthwash and/or dentifrice to cause allergic contact dermatitis in patients with cheilitis, which could lead to early diagnosis and management of this conditions.

5. Improved patient outcomes and quality of life through early diagnosis and better management of allergic contact cheilitis patients.

Conceptual framework

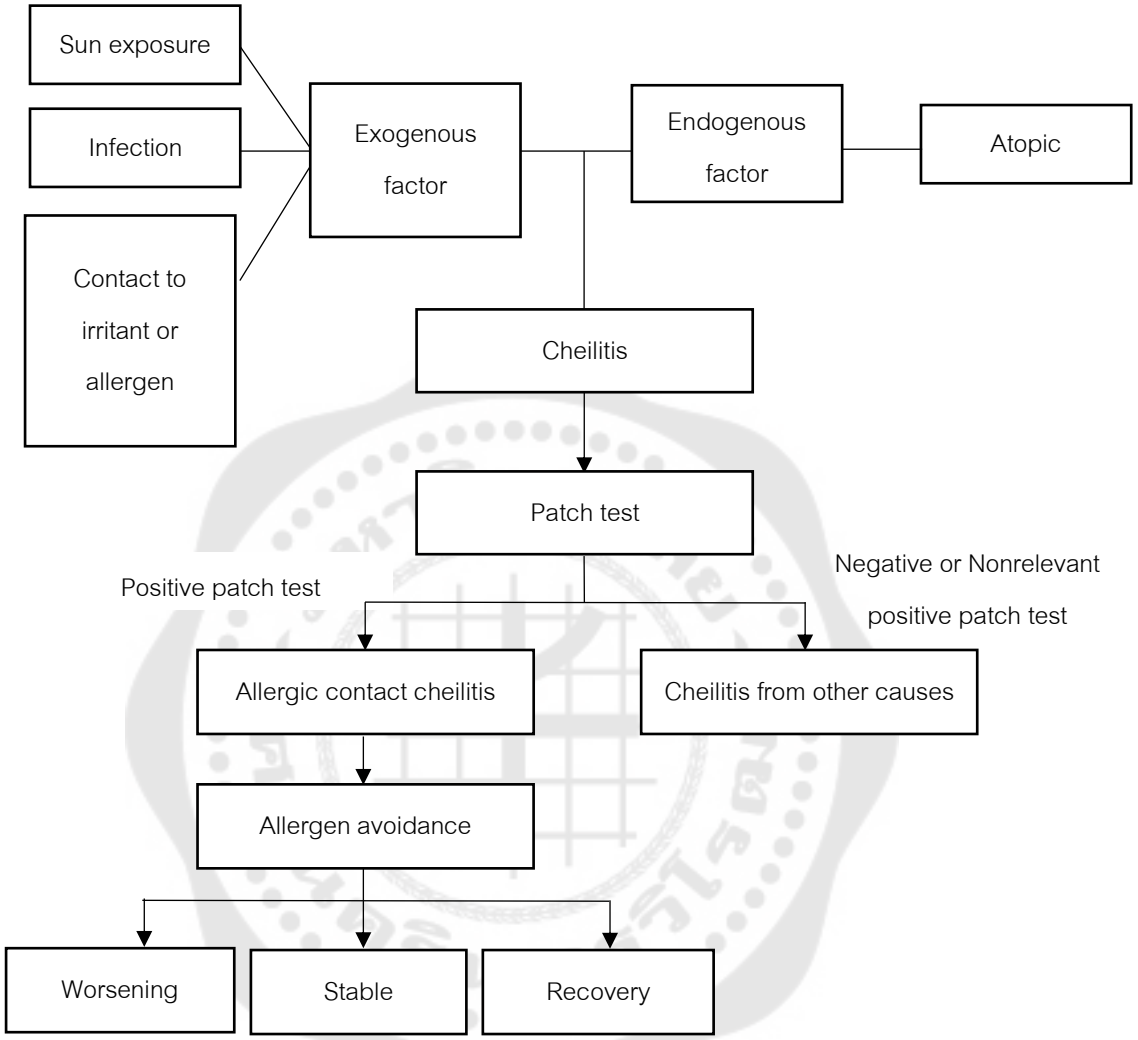

Figure 1 conceptual framework

CHAPTER 2

Literature Review

1. Cheilitis
2. Allergic contact cheilitis
3. Patch testing
4. Common allergen found in allergic contact cheilitis

1. Cheilitis

1.1 Introduction

Cheilitis is a common and multifactorial condition that can significantly impact an individual's quality of life. It is characterized by inflammation and dryness of the lips, which may progress to cracking, fissuring, and ulceration. This condition may be transient, reversible, or persistent [4] [5] [6] Cheilitis can be caused by a variety of factors, including endogenous factors, such as atopic cheilitis, or exogenous factors, such as exposure to contact irritants or allergens, chronic exposure to the sun, or infections. [7] The lips may also become affected secondarily during various skin diseases (e.g., lichen planus, angioedema, autoimmune blistering diseases, etc.) or systemic disorders (e.g., Sjögren's syndrome, sarcoidosis, etc.). [5] [6]

1.2 Types of cheilitis

There are many types of cheilitis. Liborija et al [5] proposed the latest cheilitis classification into 3 groups based on the etiology and duration of the disease: mainly reversible cheilitis, mainly irreversible cheilitis and cheilitis associated with dermatoses and systemic disease. [6]

1.2.1 Reversible cheilitis

- **Cheilitis simplex**, also known as common cheilitis or chapped lips, is a common and reversible form of cheilitis. It typically affects the lower lip and presents as cracked lips, lip fissures, or desquamation [5] [6] [8] Symptoms may include burning sensations, painful fissures, and, in some cases, the formation of crusts or bleeding.[5]

Distinguishing cheilitis simplex from actinic cheilitis based on clinical appearance alone can be challenging, particularly when crusts, fissures, or ulcers are present. In such cases, a thorough patient history is crucial for an accurate diagnosis. Factors such as the duration of lip lesions and a history of prolonged sun exposure may indicate the need for a biopsy to exclude actinic cheilitis. [5]

Frequent triggers and causes of cheilitis simplex include lip licking, especially in individuals with atopic dermatitis, repeated lip biting (cheilophagia), or wiping habits. [5] [8] Climate also plays a significant role in cheilitis development. Cold, windy, and dry weather can lead to dryness of the lips, which is aggravated by saliva moistening the lips.

- **Angular/infective cheilitis** is inflammation that occurs at the corners of the mouth and is often accompanied by erythema, deep fissures, or lacerations. Causes include infections (such as *Candida spp.* And *Staphylococcus spp.*), nutritional deficiencies, hypervitaminosis A, medications, psychiatric diseases, and inflammatory bowel diseases. [4, 6] Herpes simplex virus is a common trigger and often appears as clear, grouped papules and vesicles that form crusts as they erode and then disappear. [5] [9]

- **Eczematous cheilitis** is a common condition that causes red, scaly lesions around the mouth, often with itching and burning. It can be caused by both endogenous (such as atopic dermatitis) and exogenous factors, [10] [11] [12] [13] [14] including contact with irritants and allergens found in products like oral hygiene items, cosmetics, and dental materials. There are three subtypes of eczematous cheilitis i.e., irritant contact cheilitis, allergic contact cheilitis, and atopic cheilitis, making it challenging to diagnose without testing. Allergic contact cheilitis is more common in women and is caused by cosmetic sensitizers, lipsticks, dyes, and preservatives. Atopic cheilitis appears in patients with atopic dermatitis and is characterized by dryness, scaling, and fissuring. [6] Patch testing is a gold standard used to diagnose allergic contact cheilitis and identify the culprit allergens. The common culprit allergens for allergic contact cheilitis are metals, fragrances, and preservatives.

- **Exfoliative cheilitis** causes persistent lip desquamation, dryness, itching, and peeling mostly affected on the lower lip [15, 16] often in younger people who frequently moisturize their lips or have nutrient deficiencies. Diagnosis is based on clinical picture and exclusion of other conditions.

- **Drug-induced cheilitis** can be triggered by various medications, including isotretinoin, and requires supportive topical skin care.

1.2.2 Irreversible cheilitis

- **Actinic cheilitis** is a premalignant lip keratosis caused by chronic sun exposure, commonly seen in light-skinned individuals or those with outdoor occupations. Smoking, lip irritation, poor oral hygiene, and poor adhesion of dentures can also cause it. [6] [17, 18] [19] [20] Skin biopsy should be performed to rule out severe dysplasia or squamous cell carcinoma (SCC). [4] Actinic cheilitis presents with a whitish discoloration on the lower lip and painless thickening along the vermillion border. A precise diagnosis requires multiple biopsies. Fourier transforms infrared spectroscopy can reveal initial cancerous lesions. Differential diagnoses include granulomatous cheilitis, SCC, glandular cheilitis, and plasma cell cheilitis.

- **Granulomatous cheilitis** causes persistent lip swelling. The pathogenesis of this disease is unclear; however, the relationships to genetics, food allergies, infection, and atopy were proposed. Association with Melkersson-Rosenthal syndrome has also been reported. The patient usually presents with intermittent upper lip swelling. A lip biopsy is necessary to diagnose this condition in which clinically can mimic other diseases such as angioedema, oral Crohn's disease, sarcoidosis, or infections such as tuberculosis or histoplasmosis.

- **Glandular cheilitis** is a rare inflammatory disorder affecting minor salivary glands of the lower lip, often seen in elderly males.[6, 21] Its cause is unknown, but factors like sun exposure, poor oral hygiene, bacterial infection, and congenital predisposition may be involved.[6] Clinical manifestations are tiny red papules or edema of the lips. Abscesses or suppurative forms can be found in severe cases. Glandular cheilitis has been associated with a heightened risk for the development of squamous cell

carcinoma. Diagnosis is mainly based on the clinical manifestations. No specific histopathology changed in this disease; however confocal microscopy may be helpful for diagnosis.

- **Plasma cell cheilitis** is a rare lip inflammation disorder with an unknown etiology and is characterized by dense plasma cell infiltration.[6] It appears as an erythematous plaque or slightly raised area, often on the lower lip[6, 21]. Cutaneous lesions may be similar to other conditions such as lichen planus, allergic contact cheilitis, actinic cheilitis, SCC, or syphilis. Therefore, histological finding of bandlike plasma cell infiltration is used to diagnose plasma cell cheilitis.

1.2.3 Cheilitis associated with cutaneous/systemic diseases

Inflammatory lesions on the lip can occur with various dermatological or systemic diseases such as Lupus erythematosus, lichen planus, Sjögren syndrome, pemphigus and pemphigoid, and angioedema. A thorough examination of the oral mucosa and skin is necessary for appropriate management, as the lesion on the oral mucosa with lip involvement may be an initial presenting sign in some diseases.

- **Lupus erythematosus (LE) of the lips** is similar to atrophic actinic cheilitis both clinically and histologically. Discoid lupus erythematosus (DLE) can also involve the lips, predominantly the lower lip, and typically presents as red or white papules or plaques on the lip vermilion.[6] In systemic LE (SLE), purpuric macules, erosions, or ulcerations may be observed on the lips, along with bordered or diffuse erythema. A biopsy should be performed in cases of **LE** of the lips to check for any possibility of malignant transformations.

- **Lichen planus** usually presents with white reticular lip lesions and can be confirmed histologically, but clinical characteristics must be relied upon if histopathological characteristics are unclear or absent.

- **Sjögren syndrome** is a systemic autoimmune disease that mainly affects the salivary glands and is more common in women. Diagnosis is based on a biopsy of the salivary glands. Multispecialty collaboration along with good patient communication are crucial for excellent patient outcomes.

- **Pemphigus and pemphigoid diseases** may also manifest with lip erosions , which is more common in pemphigus than in pemphigoid patients.[6]

- **Angioedema** is common on the lips and may be related to various factors e.g. an allergy, angiotensin-converting enzyme (ACE) inhibitor use, calcium channel blocker use, etc. As angioedema can be life-threatening, it is important to determine the etiology and trigger so that the disease can be prevented or even leads to disease resolution.[6] [22]

In conclusion, cheilitis is a common condition that can be caused by various factors and can significantly impact an individual's quality of life. Allergic contact cheilitis is an essential subtype of eczematous cheilitis and is more common in women. It can be caused by cosmetic sensitizers, lipsticks, dyes, and preservatives, making it challenging to diagnose without testing. The importance of researching allergic contact cheilitis lies in the need to identify the allergens causing the reaction and provide appropriate treatment, which can significantly improve a patient's quality of life. Moreover, identifying the common culprit allergens in allergic contact cheilitis may alert governmental agencies an importance of cosmetic and personal care products ingredients regulation.

2. Allergic contact cheilitis

Allergic contact cheilitis is an inflammatory condition that affects the lips which are caused by delayed-type hypersensitivity to a specific substance (allergen).

Allergic contact cheilitis can occur as a primary disorder of the vermilion or may spread from nearby skin or from the oral mucosa. The nonkeratinized epithelium of the vermilion is more vulnerable to allergy compared to the oral mucosa due to the buffering and solvent properties of saliva. Thus, if both the oral mucosa and lips are exposed to an allergen, cheilitis may be the only manifestation. Allergic contact cheilitis has been linked to the use of various materials, such as cosmetics, moisturizers, sunscreens, nail products, oral hygiene products, dental appliances, foods, and metals. Identifying the culprit allergens and associated risk factors is important for healthcare provider in order to provide an effective management to improve patient outcomes.

2.1 Epidemiology and demographic data

The epidemiology of allergic contact cheilitis is not well established, but studies suggest that it is more common in adults than in children. Silverberg J et al [22] found cheilitis associated with age older than 40 years old, and Asian race. The prevalence varied depending on the study population and the type of allergen, but significantly increased between 2001-2002 (2.2% in primary cheilitis, 1.7% in sole cheilitis) and 2007-2018 (5.2% in primary cheilitis, 3.7% in sole cheilitis). [22] Endogenous cheilitis is the most prevalent cause of eczematous cheilitis, followed by contact cheilitis accounting for less than 50% of cases.

According to a report from Singapore, endogenous cheilitis was the most common diagnosis (53%), followed by allergic contact dermatitis (34%) in both males and females, while irritant contact dermatitis was less frequent (5.4%) [10]. Additionally, females tend to present more often for the treatment of eczematous cheilitis compared to males, with a female-to-male ratio of 9:1 in Singapore [10] and 7:3 in Australia.[23] Also, Cheng et al conducted a 10-year series from 2007 to 2018 of patch testing for cheilitis and observed a higher prevalence of cheilitis in females. Out of the patients referred with cheilitis, 71% were female, and among those diagnosed with allergic contact cheilitis (ACC), 89% were female. This finding suggests that the use of cosmetics by women may contribute to lip allergen exposure, potentially contributing to the development of cheilitis.[24]

An Italian study of 129 patients, 65% had probable or possible relevant allergens on patch testing, 19% had atopic conditions, and 16% had irritant cheilitis. Metals like nickel, chromium, and manganese were common allergens. [12]

By contrast, Freeman and Stephens analyzed 75 cheilitis cases seen in a contact dermatitis clinic, 36% had irritant cheilitis due to lip licking which is more common than allergic contact dermatitis (25%). The common allergens are fragrances and preservatives. Causative allergens present in various products such as cosmetics, medicaments, sunscreens, and toothpaste, as well as nickel in a flute player.[23]

Also, The UK report showed that only 22% out of 146 patients had relevant allergic patch test reactions, and prominent causes included flavorings, shellac, and

colophony. Additionally, 18% of those diagnosed with allergy reacted solely to their own products. [25]

Atopy, a personal history of allergic conditions, is frequently linked to cheilitis. In Singapore, studies conducted by Lim et al. and Zoli et al. revealed that approximately one-third of individuals with eczematous cheilitis had a history of atopy [10, 26], and asthma was also reported. [22] Freeman et al. conducted a study and discovered that 19% of the patients examined had atopy. [23] Additionally, Cheng et al. found 21% of cheilitis patient has atopic dermatitis.[24]

2.2 Pathogenesis

Allergic contact dermatitis (ACD) is a type IV delayed hypersensitivity reaction that develops after cutaneous exposure to sensitizing chemicals or haptens. In ACD, hapten-reactive CD4+ T lymphocytes play a central role in the pathogenesis of the disease.

Contact allergens are small molecules that can enter the skin and reach deeper layers, causing contact allergy. The allergens must be presented to T lymphocytes by antigen-presenting cells like Langerhans cells (LCs) in order to initiate the inflammatory cascade. LCs process the antigen by changing their plasma membrane, endocytosis, and protein digestion. [27, 28] T lymphocytes have receptors that complement the antigen presented by LCs and immune response-associated antigens. Interleukin-1 (IL-1) released from LCs and keratinocytes activates T lymphocytes [29]. Two mechanisms compete when exposed to contact allergens: one mediated by effector T lymphocytes, resulting in skin reactions, and the other mediated by suppressor cells, leading to tolerance. The balance between these two mechanisms determines the reactivity of the skin.

Allergic sensitization in contact dermatitis involves cytokine release after contact with an allergen, promoting contact sensitivity. Within 24 hours, LCs migrate to lymph nodes and present the antigen to T lymphocytes. Clonal proliferation of a subset of T lymphocytes occurs, which responds to the specific antigen in future exposure. Genetic susceptibility to sensitization to a specific contact allergen sets off two competing

mechanisms: allergic sensitization by effector cells and immunologic tolerance by suppressor cells.

Several factors contribute to the development of allergic contact dermatitis. These include the dose, frequency, and duration of exposure to the sensitizing agent, the route of administration, genetic polymorphisms of xenobiotic-metabolizing enzymes, and environmental factors such as psychological stress.

CD8+ cytotoxic lymphocytes [30] contribute to the elicitation of contact dermatitis, while CD4+ T cells perform regulatory functions. Allergic contact dermatitis is the inflammatory response following re-exposure to the sensitized allergen and is characterized by spongiosis and the presence of lymphocytes, histiocytes, eosinophils, and basophils. TNF-β and interferon-α induce cytotoxic effects, attract neutrophils, and stimulate T lymphocyte growth and activation. GM-CSF stimulates the activation of monocytes and neutrophils. [31] [32] [27]

Mast cells and basophils are also commonly found at sites of ACD and are involved in the release of histamine, serotonin, and leukotrienes, which can cause pruritus and vascular dilation leading to tissue edema. [33] Keratinocytes, on the other hand, produce and release various cytokines, including IL-1, GM-CSF, IL-5, and IL-8, which play important roles in activating and proliferating T cells and other immune cells. [29] In addition, involved keratinocytes produce HLA-DR antigens in the cell surface, which allows attachment of autoreactive T lymphocytes. Neurologic factors, such as neuropeptides Substance P, neurokinin A, and calcitonin gene-related peptide, and their receptors also play regulatory roles in ACD. [34]

T regulatory cells are critical in downregulating the contact sensitivity reaction, and IL-10 production by these cells is one of the mechanisms. A cell-to-cell, contact-dependent, cytokine-independent mechanism is also found. Skin memory of contact dermatitis may be due to a chemokine (CCL27) [35] that causes retention of a specific type of T cell in the skin site where the allergen was encountered. While mast cells, basophils, and keratinocytes are not essential for the development of ACD, the presence of these cells can contribute to the severity of the reaction. The pathogenesis of

ACD is complex and involves multiple cells and mediators, but the activation and proliferation of hapten-reactive T cells remain central to the development of the disease.

Allergic contact cheilitis is a type of ACD that affects the lips. It is caused by exposure to certain allergens and can result in symptoms such as dryness, cracking, and inflammation. Over time, repeated exposure to the allergen can result in a more severe reaction, which can lead to fissuring, crusting, and scaling of the lips.

The most common allergens associated with allergic contact cheilitis include metals, such as nickel, fragrances and preservatives found in cosmetics, and various plant-derived allergens such as balsam of Peru. On occasion, the ingestion of certain foods with high content of culprit allergens can cause allergic contact cheilitis.

The immune process involved in allergic contact cheilitis is complex and involves an interplay between various immune cells and mediators, resulting in a wide range of symptoms that can significantly impact an individual's quality of life. Chronic inflammation and tissue damage can occur if left untreated, leading to long-term symptoms and complications. [36]

2.3 Clinical presentation

Allergic contact cheilitis is an allergic contact dermatitis that affects the lips. The clinical presentation can vary depending on the hypersensitivity reaction.

In general, the primary symptoms of allergic contact cheilitis include redness, swelling, and itching of the lips and may be accompanied by pain and burning sensation. The lips may also become dry, cracked, and scaly. Blisters or bumps may develop.

2.4 Diagnosis of allergic contact cheilitis The diagnosis of allergic contact cheilitis typically involves a combination of a thorough medical history taking, physical examination, and patch testing.

- During the medical history taking, the healthcare provider should ask about the onset, duration, and severity of the symptoms, including when they started, how severe they are, and whether they are associated with exposure to any particular substances or activities. They may also ask about the individual's occupation, hobbies,

and exposure to different allergens, as well as any previous medical conditions or allergies.

- On physical examination, the thorough examination of the lips, surrounding skin, and oral mucosa are crucial. One should look for signs of redness, swelling, itching, and other abnormalities. They may also look for any other signs of allergic contact dermatitis in other areas of the skin.

- Patch testing is the gold standard diagnostic tool used to identify the culprit allergen causing the hypersensitivity reaction. Small amounts of different substances are applied to the skin of the individual's back or arm, and the skin is monitored for any reactions over a period of several days. This helps to identify the specific substance that triggers the allergic reaction.

3. Patch testing

3.1 Application of patch testing

- The patch test protocol typically involves applying suspected haptens onto the skin for a period of 48 hours (or 24 hours in some countries). Skin reactions are assessed at defined time points, usually 2, 3, and 4 days later. Additional reading after 7 days may reveal up to 10% of positive reactions that were previously negative. [3]

- To conduct the test, specially designed chambers on medical adhesive tape are used to apply the test substances onto the skin. Whenever possible, tests should be mounted on the patient’s back, specifically on the upper dorsum area, as this location is most convenient for both the doctor and the patient. Most patch test validation has been carried out in this area. Applying tests to other body areas, such as the arms, forearms, thighs, or abdomen, should be limited to exceptional situations and should only be performed by an experienced doctor due to difficulties with interpretation. [3]

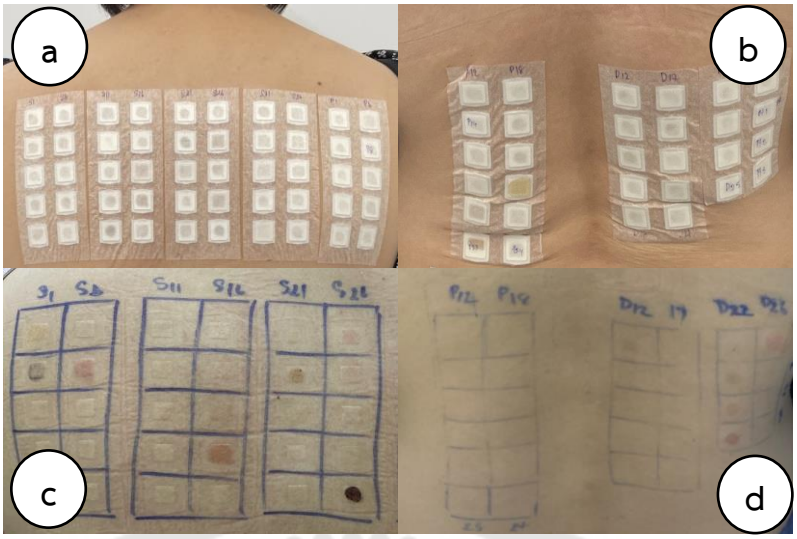

Figure 2 Illustrates the patch test process

(a), (b) patch placement on the back, (c) immediately after patch removal on Day 2 and (d) patch test site on Day 3.

3.2 Indication for patch testing [3]

- Chronic and/or recurrent itchy dermatitis (eczema) or lichenification when there is a possibility that contact allergy may be the cause or a complication of the condition.

- various inflammatory skin diseases, including atopic eczema, seborrheic dermatitis, stasis dermatitis, eczema around leg ulcers, and irritant contact dermatitis, as contact allergy (CA) and subsequent allergic contact dermatitis (ACD) can develop secondarily in these conditions.

3.3 Postponing a patch testing [37]

- Generalizes or severe active dermatitis

- Systemic immunosuppressive treatment in relevant dose where a pause is possible

- Dermatitis on the upper back or other sites chosen to apply the patch testing

- Recently used of topical corticosteroids (consider at least 7 days of postponing)

3.4 Contraindication for patch testing: [3]

- Patients with immune deficiencies disorders
- Autoimmune diseases
- Pregnancy and lactation are conditional contraindications (The safety of patch testing during pregnancy and lactation is unclear, there is no data available about the safety of the test for the mother and child)

3.5 Selection of patch test allergens

The selection of patch test allergens is guided by history such as history of allergen exposure, occupation, hobbies, and physical examination (e.g. rash localization, rash characteristics), The recommended baseline series/standard series vary from country to country based on frequent sensitizers in the country. Example of standard series are the European Baseline Series and the North American Series. (Table 1). The standard series is dynamic and is modified from time to time depending on population exposures and the prevalence of contact allergy.

In patients with allergic contact cheilitis, patch testing with only standard series is not sufficient as some relevant allergens may not be present in the standard series. Therefore, testing patients with additional series such as dental and cheilitis series, preservative series, and cosmetic series (Table 2), is important and is able to correctly predict the clinically relevant contact allergens. [3]

In addition to testing with standard test substances, it is universally accepted and beneficial to conduct patch tests using the patient's own products that are suspected to cause an allergy. As previously mentioned, the preparation of test substances from products provided by the volunteers will begin by verifying that they are not irritants, referencing the list of substances and preparing them according to the standard concentrations outlined in the book *Test Concentrations and Vehicles for 5200 Chemicals Patch Testing, 5th Edition*, by Anton C. De Groot, which is recognized as a standard internationally. (Table3) [38]

Table 1 Allergens most widely used in patch test series EBS: European baseline series, NAS: North American series

Test substance	EBS	NAS
1,3-diphenylguanidine 1.0% pet		✓
2-bromo-2-nitropropane-1,3-diol 0.5% pet		✓
2-hydroxyethyl methacrylate 2.0% pet	✓	✓
2-mercaptobenzothiazole (MBT) 2.0% pet	✓	
4-tert-butylphenolformaldehyde resin (PTBP) 1.0% pet	✓	✓
Amerchol l-101 50.0% pet		✓
Bacitracin 20.0% pet		✓
Benzisothiazolinone 0.1% pet	✓	
Benzocaine 5.0% pet		✓
Budesonide 0.01% pet	✓	
Budesonide 0.1% pet		✓
Caine mix iii 10.0% pet	✓	
Carba mix 3.0% pet		✓
Cinnamal 1.0% pet		✓
Cobalt(ii)chloride hexahydrate 1.0% pet	✓	✓
Cocamidopropyl betaine 1.0 aq		✓
Colophonium 20.0% pet	✓	✓
Compositae mix ii 5.0% pet		✓
Decyl glucoside 5.0% pet	✓	✓
Diazolidinyl urea 1.0% pet		✓
Disperse blue mix 106 / 124 1.0% pet		✓
Dmdm hydantoin 1.0% pet		✓

Table 1 Allergens most widely used in patch test series EBS: European baseline series, NAS: North American series (continued)

Test substance	EBS	NAS
Epoxy resin, bisphenol a 1.0% pet	✓	✓
yl acrylate 0.1% pet		✓
Ethylenediamine dihydrochloride 1.0% pet		✓
Formaldehyde 2.0% aq	✓	✓
Fragrance mix I 8.0% pet	✓	✓
Fragrance mix II 14.0% pet	✓	✓
Glutaral 0.5% pet		✓
Hydroperoxides of limonene 0.3% pet		✓
Hydroperoxides of linalool 1.0% pet		✓
Hydroxyisohexyl 3-cyclohexene carboxaldehyde 5.0% pet	✓	
Imidazolidinyl urea 2.0% pet		✓
Iodopropynyl butylcarbamate 0.2% pet		✓
Lanolin alcohol 30.0% pet	✓	
Mercapto mix 2.0% pet	✓	
Methyl methacrylate 2.0% pet		✓
Methyldibromo glutaronitrile 0.5% pet	✓	✓
Methylisothiazolinone+ methylchloroisothiazolinone 0.02% aq	✓	✓
Methylisothiazolinone 0.2% aq	✓	✓
Mixed dialkyl thiourea 1.0% pet		✓
N-isopropyl-n-phenyl-4-phenylenediamine (IPPD) 0 .1% pet	✓	
Neomycin sulfate 20.0% pet	✓	✓
Nickel(II)sulfate hexahydrate 2.5% pet		✓
Nickel(II)sulfate hexahydrate 5.0% pet	✓	
Oleamidopropyl dimethylamine 0.1% aq		✓
P-phenylenediamine (PPD) 1.0% pet	✓	✓
Paraben mix 12.0% pet		✓

Table 1 Allergens most widely used in patch test series EBS: European baseline series, NAS: North American series (continued)

Test substance	EBS	NAS
Paraben mix 16.0% pet	✓	
Peru balsam 25.0% pet	✓	✓
Potassium dichromate 0.25% pet		✓
Potassium dichromate 0.5% pet	✓	
Propolis 10.0% pet	✓	✓
Propylene glycol 30.0 aq		✓
Quaternium-15 2.0% pet		✓
Sesquiterpene lactone mix 0.1% pet	✓	✓
Sodium metabisulfite 1.0% pet	✓	
Textile dye mix 6.6% pet	✓	✓
Thiuram mix 1.0% pet	✓	✓
Tixocortol-21-pivalate 0.1% pet	✓	
Tixocortol-21-pivalate 1.0% pet	✓	✓
Toluenesulfonamide formaldehyde resin 10.0% pet		✓
Ylang ylang oil 2.0% pet	✓	

Table 2 SWU Standard Series, Dental and Cheilitis Series, Vehicle, and Preservative Series

No.	SWU Standard Series	No.	SWU Dental and Cheilitis Series	No.	SWU Vehicle and Preservative Series
S1	Potassium dichromate 0.5% in pet	D1	Benzyl alcohol 10.0% pet	P1	Imidazolidinylurea (Germall 115) 2.0% pet
S2	p-Phenylenediamine 1.0% in pet	D2	Glutaraldehyde 0.5% pet	P2	Quaternium-15 1.0 % pet
S3	Thiuram mix 1.0% pet	D3	Eugenol 2.0% pet	P3	2-Phenoxyethanol 1.0% pet
S4	Neomycin sulfate 20% pet	D4	Hexyl cinnamic aldehyde 10.0%	P4	Benzalkonium chloride 0.1% aq
S5	Cobalt chloride 1.0% in pet	D5	Mentha piperita oil (Peppermint oil) 2.0% pet	P5	Aluminium(III)chloride 2.0% pet
S6	Caine mix 10.0% pet	D6	Carvone 5.0% pet	P6	Cocamidopropyl betaine 1.0% pet
S7	Nickel sulfate 5.0% pet	D7	Vanillin 10.0% pet	P7	Gallate mix 1.0% pet
S8	2-Hydroxyethyl methacrylate 2.0% pet	D8	Diallyl disulfide 1.0% pet	P8	Sodium benzoate 5.0% pet
S9	Colophonium 20.0% pet	D9	BIS-GMA 2.0% pet	P9	Propylene glycol 30.0% pet
S10	Paraben mix 16.0% pet	D10	BIS-EMA 2.0% pet	P10	Tocopherol 100% pet
S11	N-Isopropyl-N'-phenyl-p-phenylenediamine 0.1% pet	D11	Methyl methacrylate 2.0% pet	P11	DMDM hydantoin 1.0% pet
S12	Lanolin (wool alcohols) 30% pet	D12	Gold sodium thiosulfate 0.5% pet		
S13	Mercapto mix 2.0% pet	D13	Copper sulfate 2.0% pet		
S14	Epoxy resin, Bisphenol A 1.0% pet	D14	Palladium chloride 2.0% pet		

Table 2 SWU Standard Series, Dental and Cheilitis Series, Vehicle, and Preservative Series (continued)

No.	SWU Standard Series	No.	SWU Dental and Cheilitis Series	No.	SWU Vehicle and Preservative Series
S15	*Myroxylon pereirae* 25.0% pet	D15	Sodium tetrachloropalladate(II)hydrate 3.0% pet		
S16	4-tert-Butylphenol formaldehyde resin 1.0% pet	D16	Mercury 0.5% pet		
S17	Mercaptobenzothiazole 2.0% pet	D17	Castor oil		
S18	Formaldehyde 2.0% aq				
S19	Fragrance mix I 8.0% pet				
S20	Sesquiterpene lactone mix 0.1% pet				
S21	Sodium metabisulfite 1.0% pet				
S22	Propolis 10% pet				
S23	MCI/MI 0.02% aq				
S24	Budesonide 0.01% pet				
S25	Tixocortol pivalate 0.1% pet				
S26	Methyldibromo glutaronitrile 0.5% pet				
S27	Fragrance mix II 14.0% in pet				
S28	Sorbitan sesquioleate 20.0% pet				

Table 2 SWU Standard Series, Dental and Cheilitis Series, Vehicle, and Preservative Series (continued)

No.	SWU Standard Series	No.	SWU Dental and Cheilitis Series	No.	SWU Vehicle and Preservative Series
S29	Methylisothiazolinone 0.20 aq				
S30	Benzisothiazolinone 0.1% pet				
S31	Textile dye mix 6.6% pet				
S32	Decyl glucoside 5.0% pet				
S33	2-Bromo-2-nitropropane-1,3-diol (Bronopol) 0.5% pet				
S34	Diazolidinyl urea 2.0% pet				
S35	2-n-Octyl-4-isothiazolin-3-one 0.1% pet				
S36	Compositae mix II 5.0% pet				
S37	Hydroperoxides of Linalool 1.0% pet				
S38	Hydroperoxides of Limonene 0.3% pet				
S39	Carba mix 3.0% pet				
S40	Sorbitan monooleate 5.0% pet				

Table 3 Guideline for patch testing cosmetic products.

Product	Concentration and vehicle
Bar soap	1% aqua
Bath products, foaming	1% aqua, 0.1% aqua
Bleaching creams	as is
Cleansing milk	10%-20% petrolatum
Face cream	as is
Foundation	as is
Fragranced products	as is
Liquid soap	5%-10% aqua or petrolatum
Lipstick	as is
Make-up cleanser	10%-20% petrolatum
Moisturizers (creams, ointments, lotions)	as is
Powder	as is
Rouge	as is
Shaving preparations	1% aqua or 5%-10% aqua or petrolatum
Shower gel	5%-10% aqua or petrolatum
Soap	1% aqua or 2% aqua
Sunscreen preparation	as is
Toothpaste	as is and 50% petrolatum

3.6 Interpretation of patch test results

An interpretation of patch test reactions is based on inspection and palpation of the morphology (erythema, infiltrate, papules, and vesicles). The globally acknowledged reading criteria of the International Contact Dermatitis Research Group (ICDRG) guidelines. [3] (Figure 3, Table 4)

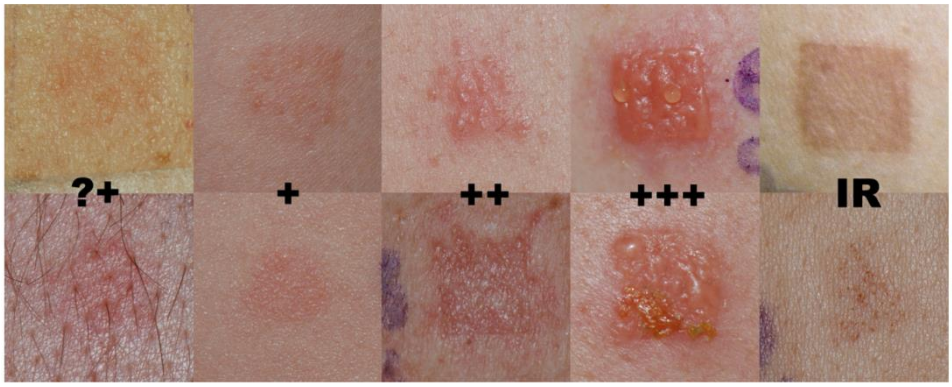

Figure 3 Grading of patch test results based on the International Contact Dermatitis Research Group (ICDRG) criteria

Table 4 Grading of patch test readings.

Notation	Description	Interpretation
- Or ∅	No skin changes in the tested are	Negative
?+	Faint, non-palpable erythema	Doubtful reaction
+	Palpable erythema -moderate edema or infiltrate, papules not present or scarce, vesicles not present	Weak reaction
++	Strong infiltrate, numerous papules, vesicles present	Strong reaction
+++	Coalescing vesicles, bullae or ulceration	Extreme reaction
NT	Not tested	
IR	Inflammation sharply limited to the exposed area, lack of infiltrate, small petechiae, pustules, and efflorescence other than papules and vesicles.	Irritant reaction

The reading and interpreting of patch test results requires training and experience, and verifying tests at a reference center may be necessary in uncertain cases. It is a challenging task to distinguish between specific allergic reactions and irritant reactions in the context of patch testing. Therefore, it is highly recommended that the task of reading and interpreting patch test results be assigned to a qualified dermatologist or allergist who possesses substantial training and experience in this field.

4. Common allergens of allergic contact cheilitis

The common culprit allergens in allergic contact cheilitis vary depending on the studied population.(Table 4) Zug et al. [38]analyzed data on cheilitis from the North American Contact Dermatitis Group, finding that of 10,061 patients patch tested, 196 had lip dermatitis, 38% were diagnosed with allergic contact dermatitis due to fragrance (30%), flavoring (23.3%), nickel (21.7%), gold (13.3%), and neomycin (11.7%), and the most relevant positive allergens are Fragrance mix, *Myroxilon pereirae*, and nickle.

Futhermore Silverberg JI et al [39] conduct a retrospective analysis involving 43,772 patients who underwent patch testing with the North American Contact Dermatitis Group (NACDG) screening series from 2001 to 2018.

The 10 NACDG screening allergens that showed the highest proportions of positive reactions in patients with primary cheilitis were as follows: [39]

1. Nickel sulphate hexahydrate, 2.5% pet. - 19.3%
2. Fragrance mix I (FMI), 8.0% pet. - 11.8%
3. Hydroperoxides of linalool, 1.0% pet. - 11.4%
4. Sodium gold thiosulfate, 0.5% pet. - 10.8%
5. Methylisothiazolinone, 0.2% aq. - 9.9%
6. Neomycin sulphate, 20.0% pet. - 9.75%
7. Thimerosal 0.1% pet. - 9.52%
8. *Myroxylon pereirae resin* (balsam of Peru), 25.0% pet. - 9.03%
9. Cobalt (6.61%) (chloride hexahydrate, 1.0% pet. - 7.27%
10. Propolis, 10.0% pet. - 1.0%

Similarly, the 10 highest NACDG screening allergens with the highest proportions of positive reactions in patients with sole cheilitis were as follows:

1. Nickel sulphate hexahydrate, 2.5% pet. - 18.5%
2. Fragrance mix I (FMI), 8.0% pet. - 12.1%
3. Hydroperoxides of linalool, 1.0% pet. - 11.7%
4. Sodium gold thiosulfate, 0.5% pet. - 11.2%
5. Thimerosal 0.1% pet. - 9.4%
6. Neomycin sulphate - 9.2%, *Myroxylon pereirae* resin (balsam of Peru), 25.0% pet. - 9.2%
7. Methylisothiazolinone, 0.2% aq. - 8.2%
8. Carmine, 2.5% pet. - 8.0%
9. Cobalt (ii) chloride hexahydrate, 1.0% pet. - 7.4%
10. Propolis, 10.0% pet. - 6.0%

Among patients experiencing primary cheilitis, the five allergens showing the highest proportions of current relevance were FMI, nickel sulphate hexahydrate, *Myroxylon pereirae* resin, methylisothiazolinone, and propolis. In the case of patients with sole cheilitis, the five allergens with the highest proportions of current relevance were nickel sulphate hexahydrate, *Myroxylon pereirae* resin, carmine, propolis, and methylisothiazolinone.

Between 2001 and 2018, primary cheilitis patients had the highest mean Significance-prevalence index number (SPIN) scores for allergens originating from nickel (jewelry [n = 182; 73.7%], miscellaneous consumer products [n = 15; 6.1%], and food products [n = 6; 2.4%]), Fragrance Mix I (FMI) (cosmetics, beauty preparations, healthcare products [n = 89; 5.6%], oral hygiene products [n = 28; 1.8%], lipsticks and lip balms [n = 20; 1.3%], and moisturizers, lotions, creams [n = 11; 0.7%]), methylisothiazolinone (shampoos, conditioners [n = 24; 3.4%], cosmetics, beauty preparations, healthcare products [n = 17; 2.4%], and moisturizers, lotions, creams [n = 6; 0.8%]), and hydroperoxide of linalool (lipsticks, lip balms [n = 9; 3.6%], cosmetics,

beauty preparations, healthcare products [n = 9; 3.6%], and miscellaneous consumer products [n = 3; 1.2%]).

Between 2015 and 2018, the most frequent sources of propolis were lipsticks, lip balms (n = 38, 3.2%), cosmetics/beauty preparations/healthcare products (n = 13, 1.1%), and oral hygiene products (n = 4, 0.3%). Similarly, the most common sources of lanolin during this period were lipsticks, lip balms (n = 39, 2.5%), cosmetics, beauty preparations, healthcare products (n = 25, 1.6%), and moisturizers/lotions/creams (n = 5, 0.3%).

Between 2001 and 2018, the main sources of allergens with the top five mean SPIN scores in patients with sole cheilitis were: (1) nickel (jewelry [n = 129; 11.1%], miscellaneous consumer products [n = 19; 1.6%], food products [n = 4; 0.3%]), (2) FMI (cosmetics, beauty preparations, healthcare products [n = 40; 3.4%], oral hygiene products [n = 24; 2.1%], and cosmetics [n = 7; 0.6%]), (3) hydroperoxide of linalool (lipsticks, lip balms [n = 7; 3.9%], cosmetics, beauty preparations, healthcare products [n = 6; 3.3%], and miscellaneous consumer products [n = 2; 1.1%]), (4) *Myroxylon pereirae* (Balsum of peru) and (5) carmine (lipsticks, lip balms [n = 6; 5.4%], makeup [n = 2; 1.8%], and cosmetics, beauty preparations, healthcare products [n = 1; 1%]).

Between 2015 and 2018, lipsticks, lip balms (n = 27; 3.1%), cosmetics, beauty preparations, healthcare products (n = 7; 0.8%), and oral hygiene products (n = 4; 0.5%) were common sources of propolis in individuals with sole cheilitis. Similarly, lipsticks, lip balms (n = 36; 2.7%), cosmetics, beauty preparations, healthcare products (n = 8; 0.7%), and moisturizers, lotions, creams (n = 4; 0.3%) were common sources of lanolin [39]

Table 5 Literature review on patch testing in cheilitis patient

Author	Year published	Location	Years of analysis	Population size (n)	Patch test results	Top relevant allergen
Kanokrungsee et al [40]	2023	Thailand	14 years; 2007-2021 .	5366 patients referred for patch testing, with 410 patients (7.6%) diagnosed with cheilitis. 32% of these were diagnosed with ACC.	ACC patients were more likely to be young, female, have a disease duration <3 months, no underlying disease, and a white-collar job.	Patient's products (73.3%), nickel sulfate (29.8%), potassium dichromate (14.5%), castor oil (14.3%) and benzalkonium chloride (13.0%). Lip cosmetics and toothpastes were major ACC sources.
Siverberg et al [41]	2022	United states	17 years: 2001-2018	43,772 patients tested, with 2094 (4.8%) having lip dermatitis; 1583 (3.6%) with primary lip site, and 1167 (2.7%) with sole lip site.	60% of cheilitis patients had positive patch-test reactions, compared to 65% in non-cheilitis patients. Over 25% of cheilitis cases reacted to non-NACDG allergens.	Nickel sulfate., Fragrance mix I, 8.0% pet. Hydroperoxide of linalool, 1% pet., *Myroxylon pereirae* Resin
Cheng et al [10]	2019	Australia	10 years; 2007-2017	1584 patients, 91 with cheilitis (5.7%)	Patients with cheilitis were more likely to have at least one positive patch-test reaction. However, there were no differences in the mean number of patch-test reactions between the groups. 17% of cheilitis patients tested had a relevant allergen identified. Additionally, 82% of patients referred for cheilitis were female.	Top relevant allergens Personal products including lip balms, lipsticks, toothpaste, and a topical antiviral cream (13% positive and relevant) and sunscreens containing benzophenone 3 & 4

Table 5 Literature review on patch testing in cheilitis patient (continued)

Author	Year published	Location	Years of analysis	Population size (n)	Patch test results	Top relevant allergen
O'Gorman and Torgerson [11]	2016	United states	10 years: 2001-2011	91 patients. 41 with cheilitis (45%)	Significant female population (77%). 41(45%) had a final diagnosis of ACC.	Fragrance mix, *Myroxylon pereirae* resin, dodecyl gallate, octyl gallate and benzoic acid
Milanesi et al [14]	2016	Italy	4 years: 2009-2013	38 patients with cheilitis (12 males, 26 females)	A positive reaction to the patch test was observed in 20 patients, representing 52.6% of the cohort.	Fragrance mix, eugenol, MI/MCI, propolis and Lyral 5%
Lavy et al.[42]	2009	Israel	1.5 years: 2007-2008	44 patients. 24 with cheilitis (55%) and 20 with contact dermatitis but without cheilitis	Patients with cheilitis exhibited a significantly higher average number of positive reactions to personal toothpaste compared to the control group. However, no significant difference was found in the number of relevant reactions between the two groups.	Personal toothpaste
Zug et al [43]	2008	United States	4 years: 2001-2004	10 061 patients, 196 with cheilitis (2%)	Clinically relevant positive allergens were more prevalent in the overall patch-tested population (50.7%, n = 5096) compared to the lip-only subgroup.	Fragrance mix, *Myroxylon pereirae* and nickel sulfate
Schena et al. [12]	2008	Italy	5 years: 2001-2006	129 patients with cheilitis (106 females, 23 males)	A total of 84 patients (65%) exhibited positive patch-test reactions with 'possible' or 'probable' relevance. Of these, the population was predominantly female (65.1%; 72 females), with a median age of 40 years.	Nickel, fragrances, balsam of Peru, chromium salts, and manganese salts, present primarily in cosmetics, dental materials, and oral hygiene products

Table 5 Literature review on patch testing in cheilitis patient (continued)

Author	Year published	Location	Years of analysis	Population size (n)	Patch test results	Top relevant allergen
Katsarou et al [44]	2008	Greece	14 years: 1992-2006	10,580 patients patch tested. 106 patients with cheilitis(1%)	Out of the 106 patients, 80 were female (75.5%), and 64% of these patients exhibited positive patch-test reactions.	Tosylamide/formaldehyde resin 10% Nickel sulfate 5%, Benzoyl peroxide 1% and, thiomersal 0.1%, and
ML. García-Melgares et al	2007	Spain	21 years: 1985-2006	6441 patients were patch tested, with 63% cheilitis.	Of the 1173 patients tested for octyl gallate, propyl gallate, and dodecyl gallate, 46 patients (3.92%) tested positive, with sensitization rates of 3.53% for the preservative series and 10.14% for the bakery series.	propyl gallate, octyl gallate, dodecyl gallate
Zoli et al [26]	2006	Italy	4 years: 2001-2005	83 patients with cheilitis or perioral eczema (59 females and 24 males)		Fragrance mix, nickel sulfate, methyldibromo glutaronitrile, *Myroxylon pereirae*, and own cosmetic
Strauss and orton [25]	2003	United Kingdom	19 years: 1982-2001	9,980 patients were patch tested and 146 (1.5%) had cheilitis as the main complaint	A total of 22 patients (15%) had positive patch-test reactions considered relevant to the cheilitis, with 21 of them (95%) being female.	Fragrance mix, shellac, colophonium, *Myroxylon pereirae*, and own lipstick
Lim and Goh [10]	2000	Singapore	3 years; 1996-1999	202 patients with cheilitis, with 182 females (90%) and 20 males (10%)		Own cosmetics, ricinoleic acid (castor oil), own toothpaste, fragrance mix, and *Myroxylon pereirae*

Table 5 Literature review on patch testing in cheilitis patient (continued)

Author	Year published	Location	Years of analysis	Population size (n)	Patch test results	Top relevant allergen
Francalanci et al. [45]	2000	Italy	1 year: June 1997-1998	54 patients (33 [61%] females, [39%] males)	In females, lip cosmetics were the most common cause of allergic contact cheilitis, accounting for 54% (44/81) of cases, followed by toothpastes at 21% (17/81) and topical medications at 7% (6/81). In males, toothpastes were the most frequent cause of allergic contact cheilitis.	Ricinoleic acid and the patient's own lip products
Freeman and Stephens[23]	1999	Australia	6 years; 1991-1997	75 patients (3.4% of patients seen at the Contact and Occupational Dermatitis Clinic of the Skin and Cancer Foundation)	Of the 53 patients (67%) who were female, the age range was 9 to 79 years. Among the cases, 36% were attributed to irritant contact dermatitis (ICD), 25% to allergic contact dermatitis (ACD), 19% to atopic eczema, and 9% had dermatitis of unknown cause.	Neomycin, fragrance mix, wool alcohols, and oxybenzone
Kanthraj et a| [46]	1999	India	3 months; 1999	8 patients with cheilitis (2 males, 6 females)	The allergens identified included Propyl and Octyl gallates (antioxidants), Thimerosal (preservative), Sorbitan monooleate (emulsifier in cosmetics), and Mercury.	N/A
Lim et al. [47]	1992	Singapore	2 years; 1989-1991	27 patients (21 females, 6 males) with cheilitis	Allergic contact cheilitis was suspected in 16 of the 27 patients (59%), with lipstick identified as the cause in 11 cases, toothpaste in 8, fragrance in 1, and dental braces in 1.	Toothpaste, lipstick, and nickel

Few studies on the Asian population were conducted. For example, A retrospective epidemiologic study conducted by C.L. Goh [10] in Singapore on 202 patients with eczematous cheilitis attending a patch test clinic from 1996-1999 revealed that lip cosmetics, including lipsticks, lip balms, and other cosmetic preparations, were the most common causes of allergic contact cheilitis (55.6%). Among these, ricinoleic acid, the main constituent of castor oil, was the most common known contact allergen, causing cheilitis in 10.4% of cases. Colophony, commonly used in lip cosmetics for a glossy appearance, was an uncommon allergen. Sunscreens were also uncommon causes of allergic contact cheilitis.

Toothpaste was the second most common cause of contact cheilitis, accounting for 25.9% of cases. Flavors (such as cinnamal, cinnamon oil, and peppermint) and preservatives (such as parabens) being common allergens in toothpaste. One patient was sensitive to L-carvone, a flavoring found in spearmint, which is commonly used in toothpastes. Tartar-control toothpastes did not cause any irritant reactions in this study.

Topical medication was the third most common cause of contact cheilitis, accounting for 7% of cases, with neomycin, quinolines, and traditional Chinese medications being the most common contact allergens. Nickel, from lipstick casing, spectacle frames, and earrings, was a rarer allergen

Moreover, Lim et al[47] conducted a retrospective study in Singapore of 27 patients with cheilitis reporting that lipstick, toothpaste, and nickel are the main causes of allergic contact cheilitis. Patch testing detected responsible allergens in 9 patients, with 5 reacting to popular toothpaste brands (Darlie and Colgate). Fluoride, flavorings, and preservatives have been implicated in toothpaste dermatitis.

One study conducted in India, patch testing in 8 patients with cheilitis identified culprits allergens as follows: propyl and octyl gallates (antioxidants), thimerosal (a preservative), sorbitan monooleate (an emulsifier, commonly found in cosmetics), and mercury. [48]

Contact allergy to ingredient in toothpaste

Toothpaste, also known as dentifrices, play a vital role in maintaining oral health and aesthetics. They are intricate formulations comprising over 20 ingredients, and their chemical composition continuously evolves due to competition, innovations, and scientific advancements by manufacturers. [49-52] Some ingredients in toothpaste formulations have the potential to cause allergic contact cheilitis. Common allergens include certain flavoring agents, preservatives, and additives. If someone experiences persistent lip irritation or other symptoms after using a particular toothpaste, it's essential to discontinue use and seek professional advice for proper evaluation and identification of the allergen.

The key functional classes of toothpaste ingredients include:

1. **Mild abrasives**: To remove debris and surface stains from teeth gently.

2. **Fluoride:** Strengthening tooth enamel and preventing tooth decay (caries) through remineralization.

3. **Humectants**: To prevent water loss and maintain toothpaste consistency.

4. **Flavoring agents**: Masking the taste of surfactants and providing breath freshening with cooling, heating, or tingling sensations. Mint flavors like menthol, peppermint oil, and spearmint oil are commonly used. [50]

5. **Sweeteners:** Artificial sweeteners to enhance the taste of toothpaste.

6. **Thickening agents or binders**: Stabilizing the toothpaste formula.

7. **Detergents**: Creating foaming action, with sodium lauryl sulfate being the most common surfactant used. [50]

8. **Coloring materials**: Improving toothpaste appearance with white bases, sometimes combined with colored stripes to suggest multiple benefits. Titanium dioxide creates whiteness, while artificial colorants add colored stripes or cores. [50]

9. Water: Facilitating the dissolution of inorganic active ingredients, particularly fluorides.

Example chemicals in these functional classes of toothpaste ingredients are shown in Table 6.

Table 6 Example chemicals in the functional classes of toothpaste ingredients

Functional Class	Examples of Chemicals [49, 51, 52]
Abrasives	Alumina (aluminium oxide), calcium carbonate, calcium pyrophosphate, dicalcium phosphate dehydrate, (hydrated) silica, magnesium carbonate, sodium bicarbonate, sodium metaphosphate
Fluoride	Inorganic: sodium fluoride, sodium monofluorophosphate, stannous fluoride (SnF2); organic: octadecenylammonium fluoride (dectaflur), olaflur
Humectants	Erythritol, glycerin, isomalt, propylene glycol, sorbitol, xylitol
Flavoring agents	Cinnamon, herbal, lemon, and mint flavors (menthol, peppermint oil, spearmint oil)
Sweeteners	Sodium saccharin, sucralose, xylitol
Thickening agents	Crosscarmellose (carboxymethylcellulose), crosslinked polyacrylates, hydroxyethylcellulose, natural gums (agar, carrageenan, xanthan), seaweed colloids, thickening silicas
Detergents	Cocamidopropyl betaine, sodium cocoyl sarcosinate, sodium lauroyl sarcosinate, sodium lauryl sulfate, sodium C14-16 olefin sulfonate, steareth-30
Coloring materials	Artificial colorants, titanium dioxide (white)
Water	

Some toothpaste includes specific ingredients to address particular dental concerns: [49-52]

1. **Periodontal disease (gingivitis):** Natural plant extracts, essential oils, enzymes, vitamins, and antibacterial substances like chlorhexidine, triclosan, and triclosan copolymers may be used to prevent and treat gingivitis.

2. **Malodor:** Toothpastes combat bad breath by utilizing anti malodor agents like zinc citrate and zinc chloride, which react with volatile sulfur compounds to neutralize odors. [50]

3. **Tartar/calculus**: Antitartar agents containing sodium or potassium salts of tripolyphosphate and zinc salts help prevent the hardening of plaque into tartar. [50]

4. **Whitening/bleaching:** Whitening toothpaste removes stained plaque, potentially using enzymes, abrasive substances, or pyrophosphates to absorb stain molecules. Optical whiteners like blue covarine may also be used. However, the efficacy of bleaching toothpastes with hydrogen peroxide or calcium peroxide is uncertain.

5. **Dentin hypersensitivity**: Toothpastes for sensitive teeth desensitize nerves or physically block dentinal tubules using potassium salts, strontium salts, stannous fluoride, and other compounds. [50]

6. **Dry mouth:** Toothpastes containing olive oil, betaine, and xylitol help stimulate salivary secretion for individuals with dry mouth. [52]

Published cases of contact allergic reactions to toothpaste ingredients are summarized in Table 7.

Table 7 Summary of published cases of contact allergic reactions from ingredients in toothpastes

Author	Sex/Age, Clinical Picture	Allergen(s)	Comments
Foti et al [53]	F/50 Cheilitis	Amine fluoride, 5% water (active ingredients 0.9%)	Italy (2014): Elmex Erosion Protection toothpaste (3% in pet, ROAT) was positive, with symptoms clearing and no relapse after discontinuation.
Zirwas and Otto [54]	M/81 Cheilitis, dermatitis around the mouth	Flavorings	United States (2010): Positive patch tests to fragrance mix I, cinnamic alcohol, and Arm & Hammer toothpaste (brand unverified); symptoms resolved after switching toothpaste.
Poon and Freeman [55]	F/63 Cheilitis	Anethole 2% pet	Australia (2006): Positive reaction to anethole, presumed culprit, though its presence in spearmint oil was not confirmed; symptoms resolved after cessation.
Agar and Freeman [56]	F/10 Cheilitis	Cocamidopropyl betaine 1% water	Australia (2005): No patch test on Colgate 2-in-1 toothpaste; avoidance led to symptom resolution within weeks.
Corazza et al [57]	F/68 Cheilitis	Carvone 5% pet	Italy (2002): The patient reacted to carvone and two toothpastes (Colgate and AZ protezione carie), tested undiluted. Carvone presence was confirmed by chromatography; lesions healed after stopping the toothpastes.
Lee et al[58]	F/38 Erythematous edematous patches on and around the lips, F/62 Erythematous scaly patches around the lips	Sodium lauryl sulfate 1% and 0.1% water	Korea (2000); the patient reacted to toothpaste 2% in water, Korea (2000); the patient reacted to toothpaste 1% in water

Table 7 Summary of published cases of contact allergic reactions from ingredients in toothpastes (continued)

Author	Sex/Age, Clinical Picture	Allergen(s)	Comments
Skrebova et al [59]	F/71 Sore mouth, cheilitis, angular cheilitis, eczema around the mouth	Spearmint oil 5% pet	Denmark (1998): Toothpastes were not tested, and the presence of spearmint oil was not confirmed.
Franks [60]	F/64 Dry mouth, erythema and desquamation of oral mucosa, cheilitis, perioral eczema, loss of taste	Anethole 5% pet	United Kingdom (1998): The patient reacted to Kingfisher toothpaste (2% in water) but not to Colgate toothpaste (2% in water). Colgate contained anethole, and Kingfisher contained fennel, a natural source of anethole. Symptoms slowly resolved after avoiding anethole.
Worm et al [61]	F/58 Erosive (angular) cheilitis	L-carvone 0.27% and 0.067% vehicle? spearmint oil 1% vehicle?	Germany (1998): The patient tested positive for Colgate toothpaste after tape stripping and was also allergic to mouthwash with the same allergens. Symptoms resolved with flavor-free toothpaste.
Aguirre et al [62]	M/28 Edematous cheilitis	Sodium benzoate 1% and 2% aq and pet	Spain (1993): Positive patch test to Enciodontyl toothpaste; cheilitis exacerbated by sodium benzoate in a mucolytic syrup. Symptoms worsened each morning after brushing, likely due to immediate contact reaction to sodium benzoate, though not suggested by the authors.

Table 7 Summary of published cases of contact allergic reactions from ingredients in toothpastes[(continued)

Author	Sex/Age, Clinical Picture	Allergen(s)	Comments
Macháckova and Smíd [63]	M/71 Cheilitis	Flavorings 1% alc and chloroacetamide 0.2% water	Czechoslovakia (1991): The patient reacted to two toothpastes tested as is, specifically to the flavors and the preservative chloroacetamide (present in one or both). Symptoms cleared after discontinuing the use of these toothpastes.
Maibach[64]	F/82 Cheilitis	Cinnamal 1% pet	United States (1986): The patient used a sunscreen lipstick and toothpaste containing cinnamal. The toothpaste was not patch tested, but symptoms cleared after avoidance.
Ormerod and Main [65]	F/47 Gingivitis, moderate cheilitis	Formaldehyde 2% water	United Kingdom (1985): The patient, pre-sensitized, developed gingivitis and moderate cheilitis within 2 days of using McLean sensitive teeth formula containing 1.3% formalin (formaldehyde solution).
Grattan and Peachey [66]	F/65 Sore mouth, cheilitis	Spearmint oil 1% pet, l-carvone 1% pet, anethole 2% pet	United Kingdom (1985): The patient reacted to two toothpastes (10% pet). One contained spearmint oil and carvone, while the other contained spearmint flavor and anethole (not found in spearmint oil). The eruption resolved after discontinuing the toothpastes with spearmint oil. In the control group (30 participants), all tested undiluted with the two toothpastes, and 9 showed slight irritant reactions.

Table 7 Summary of published cases of contact allergic reactions from ingredients in toothpastes (continued)

Author	Sex/Age, Clinical Picture	Allergen(s)	Comments
Hausen [67]	M/74 Cheilitis, erythema, and burning of the oral mucosa	L-Carvone 1% DEP; peppermint oil 0.5% DEP	Germany (1984): The patient had a very strong reaction to L-carvone and a weak cross-reaction to D-carvone, with L-carvone making up 20%-30% of the flavor. The patient tested positive for the toothpaste as is and experienced recurrence of cheilitis from refreshment lozenges. Control tests with L-carvone and peppermint oil were negative.
Drake and Maibach[68]	M/52 Cheilitis, stomatitis, eczema of the fingers of the left hand	Cinnamal 1% pet, cinnamon bark oil and cassia oil 1% pet	United States (1976): The patient reacted to toothpaste (5% in pet).
Magnusson and Wilkinson [69]	M/40 Cheilitis	Cassia oil, cinnamal	Positive reaction to the toothpaste as is; clearing after stopping, exacerbation after using toothpaste again
Fisher and Tobin [70]	F/29 (Angular) cheilitis, glossitis, F/20 Angular cheilitis, perioral eczema, glossitis, stomatitis, M/53 Stomatitis, glossitis, perioral eczema, cheilitis	Dichlorophene 5% pet	**United States (1953);** ammoniated toothpaste; the toothpaste was tested and positive in 2; in all 3 patients, prompt relief after discontinuation and recurrence after provocation; in 1 patient, all other constituents were tested and negative; the authors mentioned 4 more such patients, details not provided; dichlorophene 5% was negative in controls
Fisher and Lipton [71]	M/53 (Angular) cheilitis, glossitis, marked loss of taste	Dichlorophene 5% pet	**United States (1951);** ammoniated toothpaste, the toothpaste was positive; 10 controls were negative to the toothpaste; prompt clearance after avoiding the toothpaste and recurrence with reuse

CHAPTER 3

Research design and Methods

Study design

A cross-sectional descriptive study

Target population

All patients with an unidentified cause of cheilitis who visit the Dermatology Clinic, Department of Dermatology, Srinakharinwirot University (SWU) from January 2024 to December 2024 will be enrolled in this study. All participants will be patch tested to SWU Baseline Series (Modified European Baseline Series), SWU Vehicles, Preservative and other supplemental allergen series, SWU Dental and Cheilitis Series, and up to 10 patients' own products. Positive and relevant reactions will be recorded.

Demographic data including age, gender, history of atopic dermatitis and/or other atopy, underlying diseases, hobbies, occupation, and site of dermatitis will be collected.

Sample size calculation

This is a cross-sectional prospective study, aimed at determining the clinically relevant allergens in patients with allergic contact cheilitis. All consecutive patients who visit the Dermatology Clinic, Department of Dermatology, Srinakharinwirot University from January 2024 to December 2024 will be inquired for their voluntarily participate in the study and will be enrolled.

SPIN analysis

The Significance-Prevalence Index Number (SPIN) was calculated using a weighted formula that combines the prevalence of an allergen with its clinical relevance. This index was designed to assess the relative importance of each allergen by considering both the proportion of the population affected and the degree of relevance based on clinical assessment. The calculation used was as follows:

SPIN=(Prevalence of the allergen)×([1×percentage with definite relevance] +[0.66×percentage with probable relevance]+[0.33×percentage with possible relevance])×10

Study criteria

Inclusion criteria

1. Subjects must be at least 18 years of age.
2. Subjects must be suspected of having allergic contact cheilitis.
3. Subjects must be willing and able to comply with the requirements of the study protocol.
4. Subjects voluntarily agree to participate in this research project and have documented their consent by signing the informed consent form.

Exclusion criteria

1. Participants with any medical condition that could potentially interfere with the results of the patch test, including
    1.1 Severe or generalized active dermatitis
    1.2 Use of systemic immunosuppressive agents such as corticosteroids, azathioprine, or cyclosporine in relevant doses
    1.3 Dermatitis on the back or other sites selected for the patch test
    1.4 Recent ultraviolet exposure of the test area
    1.5 Treatment with topical corticosteroids within 14 days of the patch test.
2. Female participants who are pregnant or lactating.
3. Participants with a history of anaphylaxis.

Discontinuation criteria

1. Patients who have adverse effects during the study
    - Infection
    - Anaphylaxis
2. Patients who prefer to quit the study after participating.

Research instrument

1. Patch testing
    - SWU Baseline Series
    - SWU Vehicle, Preservative, and other supplemental allergen Series
    - SWU Dental and Cheilitis Series
    - Patient's personal products (up to 10 items)
    - Fin chamber
    - Micropore surgical tape
2. Marker pen for identifying the number of allergens
3. High-resolution digital camera
4. Instruction form
5. Case record form
    - Patient's general information
    - Patch testing record form
    - Side effect record form
    - Dermatology life quality index (DLQI) form
6. Patient information sheet
7. Informed consent form
8. Appointment card

Protocol flow chart

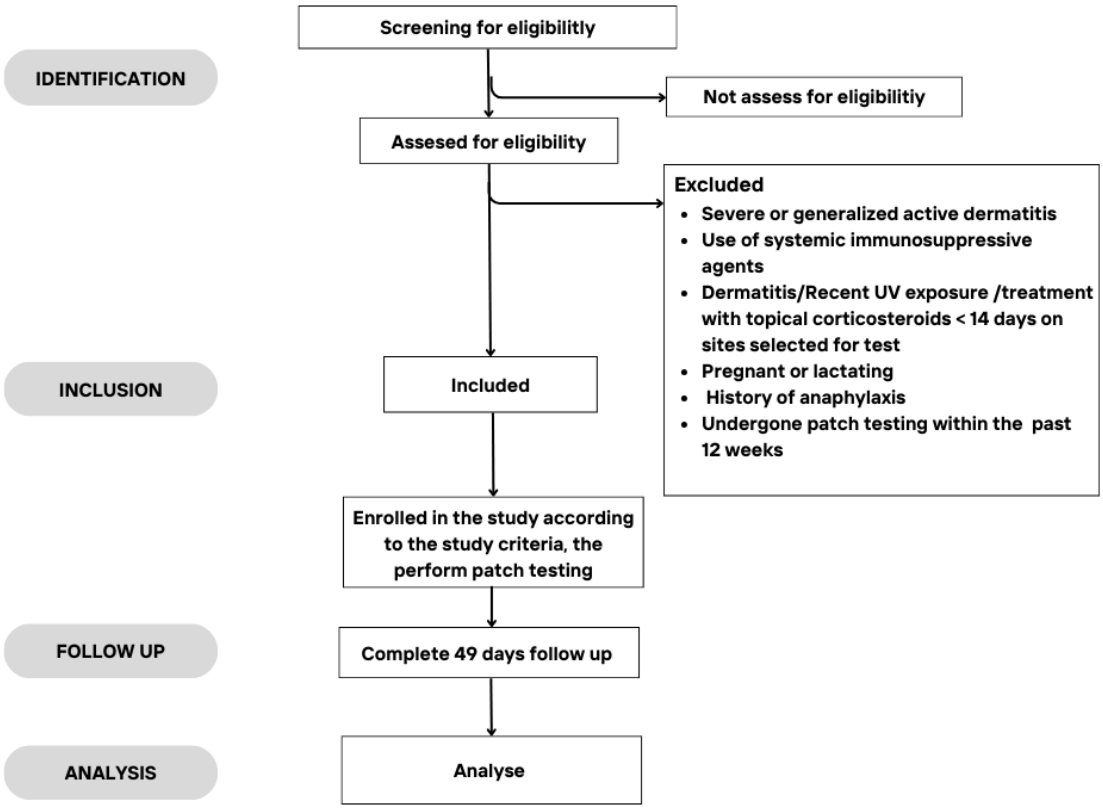

Figure 4 Protocol flow chart

Study process

Baseline / Screening visit (Day -30 to Day 0)

To initiate the recruitment of volunteers for research, the initial step is to select eligible individuals according to specific inclusion criteria. Subsequently, the investigator responsible for the study must provide a detailed and comprehensive explanation of the research process, including the potential advantages, disadvantages, and side effects that may arise during the study. Additionally, the investigator must explain the measures that will be taken to mitigate any risks and provide information on follow-up procedures. Upon receiving this information, the prospective volunteer may make an informed decision about participating in the study and demonstrate their commitment by signing a consent form. Once the volunteer has provided consent, the investigator may proceed with conducting a thorough history taking and physical examination. Medical history, surgical history, medications, demographics, and physical exam findings including vital signs and areas for patch testing should be recorded accurately in the case record forms.

Once the history taking and physical examination are complete and all relevant information has been recorded. The investigator will proceed with patch placement or will make an appointment for patch placement if the participant wishes to have the placement done later.

Patch placement visit (Day 0)

The following procedures will be performed on the day of the patch test application.

- Photograph the patch test site pre- and post- patch placement, using a high-resolution digital camera

- Patch placement with the following allergen series: (1) SWU Baseline Series, (2) SWU Vehicle, Preservative, and other supplemental allergen Series, (3) SWU Dental and Cheilitis Series, and (4) up to 10 Patient's personal products

-In-clinic observation for 30 minutes to assess for immediate adverse events/complications

- Provide a pamphlet of post-patch test instruction

- Assess the patient's quality of life by using the Dermatology life quality index (DLQI

48-hour reading visits (Day 2)

- Photograph the patch test site before the patch removal from the test site, using a high-resolution digital camera

- Remove all the patches and wait 15-30 minutes to allow the resolution of pressure effects.

- Photograph the patch test site before perform reading, using a high-resolution digital camera

- Grading the patch test reactions will be performed by using reading criteria of ICDRG[3] as previously mentioned (Figure 3 and Table 4).

- Assess for adverse events/complications following the patch testing

72-hour and 168-hour reading visits (Day 3, and Day 7)

- Photograph the patch test site before perform reading, using a high-resolution digital camera

- Grading the patch test reactions will be performed by using reading criteria of ICDRG[3] as previously mentioned (Figure 3 and Table 4).

- At day 7, the physician informs the patch test result to the volunteer. If any positive reactions occur, the physician will describe and give a recommended information form in order to avoid the positive relevant allergen.

- Assess for adverse events/complications following the patch testing

Follow-up visit (Day 14)

A follow-up visit will occur on day 14 or at any time the subject or the investigators believes an adverse event has occurred. Patients will have a grace period of 3 days after each follow-up visit to complete case record form.

The following procedures will be performed at all follow-up visits, unless otherwise noted:

- Examine the patch test sites

- Assess for adverse events/complication following the patch testing

- Inquire if any new medication use. Document all current medications, including over-the-counter medications and herbal medications

- Photograph the patch test site using a high-resolution digital camera if any dermatitis occurs

Final Study Visit (day 49)

The following procedures will be performed at the final post-patch testing visit:

- Assess for adverse events/complications following the patch testing
- Photograph the patch test site using a high-resolution digital camera if any dermatitis occurs
- Assess the patient's quality of life by using the Dermatology life quality index (DLQI)

Unscheduled Visit

The following procedures will be performed if the subject presents to the clinic at any other time point not specified above:

- Assess for adverse events/complications following the patch testing
- Inquire if any new medication use. Document all current medications, including medications over the counter and herbal medications
- Examine the patch test sites
- Photograph the patch test site using a high-resolution digital camera if any dermatitis occurs

Study outcome

Primary Outcome:

Positive relevant allergens present in allergic contact cheilitis in the study population

Secondary Outcomes:

1. Patient characteristics and demographic data in patients with allergic contact cheilitis
2. Patient's Quality of life in patients with allergic contact cheilitis by using the Dermatology life quality index (DLQI)

3. Compare patient's quality of life pre- and post-allergen avoidance in the patients with a definitive diagnosis of allergic contact cheilitis.

- Pre- and post-patch testing and allergen avoidance, patients will be asked to complete the Dermatology life quality index (DLQI) questionnaire (Figure 5, Table 8) independently. The questionnaire comprises 10 questions that assess the impact of skin conditions on patients' quality of life

3 = very much

2 = a lot

1 = little

0 = not at all, no relevant, and no answer

Sum scores of the 10 questions are interpreted as detailed in Table 8.

Table 8 Dermatology life quality index (DLQI) score

The DLQI scores	Interpretation
0-1	No effect at all on patient's life
2-5	Small effect on patient's life
6-10	Moderate effect on patient's life
11-20	Very large effect on patient's life
21-30	*Extremely large effect on patient's life*

DLQI Thai version

แบบสอบถามวัดคุณภาพชีวิตของผู้ป่วยโรคผิวหนัง
(ข้อมูลของท่านจะเป็นความลับ ไม่ถูกนำไปเปิดเผยเป็นรายบุคคลต่อผู้ใดทั้งสิ้น)

ชื่อ _____ H.N. ____/_____ DLQI Score: _____

เพศ ชาย หญิง อายุ _____ ปี อาชีพ_____

Study No. _____วันที่ ___ / _____ / _____ Diagnosis_____

จุดประสงค์ของแบบสอบถามนี้ เพื่อประเมินว่า ผื่นผิวหนังทำให้เกิดปัญหากับคุณมากน้อยเพียงใดในช่วงหนึ่งสัปดาห์ที่ผ่านมา? **กรุณาตอบคำถามโดยทำเครื่องหมาย ✔ ลงในช่องทางขวามือ (ขอความกรุณาตอบคำถามทุกข้อ)**		
1. ช่วงสัปดาห์ที่ผ่านมา คุณมีอาการคัน, เจ็บ, ปวด, หรือปวดเสียว ที่ผิวหนัง มากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	
2. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้คุณรู้สึกอับอาย, ขาดความมั่นใจ มากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	
3. ในช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้คุณมีปัญหาในการออกจากบ้านไปจับจ่ายซื้อสินค้า, ดูแลบ้าน หรือดูแลสวน มากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	ไม่มีความเกี่ยวข้อง
4. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังของคุณ มีผลกระทบต่อการเลือกเสื้อผ้าที่จะสวมใส่ มากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	ไม่มีความเกี่ยวข้อง
5. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังของคุณ มีผลกระทบต่อการเข้าสังคม หรือต่อกิจกรรมในยามว่าง มากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	ไม่มีความเกี่ยวข้อง
6. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังมีผลกระทบต่อการเล่นกีฬา การออกกำลังกายของคุณ มากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	ไม่มีความเกี่ยวข้อง
7. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังมีผลทำให้คุณขาดงานหรือขาดเรียนหรือไม่	มี ไม่มี	ไม่มีความเกี่ยวข้อง
ถ้า "ไม่มี" ในช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้มีคุณมีปัญหาในการทำงาน หรือ การเรียน มากน้อยเพียงใด	ปานกลาง เล็กน้อย ไม่มีเลย	
8. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังของคุณ ได้สร้างปัญหาให้กับคู่ครอง หรือญาติหรือเพื่อนสนิท มากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	ไม่มีความเกี่ยวข้อง
9. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้คุณมีปัญหาในการมีเพศสัมพันธ์ มากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	ไม่มีความเกี่ยวข้อง
10. ช่วงสัปดาห์ที่ผ่านมา การรักษาผื่นผิวหนังก่อให้เกิดปัญหาแก่คุณ มากน้อยเพียงใด เช่น ทำให้มีการเปรอะเปื้อนในบ้าน, การรักษาทำให้เสียเวลา เป็นต้น	มาก ปานกลาง เล็กน้อย ไม่มีเลย	ไม่มีความเกี่ยวข้อง

Figure 5 Dermatology life quality index (DLQI) questionnaires in Thai version

Research process

The study process for this research was outlined in Table 9, structured by day of visit.

Table 9 Research process

Study process	Baseline/Screening (Day -30 to Day 0)	Day 0	Day 2	Day 3	Day 7	Day 14	Day 49
History taking and physical examination	✓						
Photograph the patch test site		✓	✓	✓	✓	✓	✓
Patch placement		✓					
Reading the patch test			✓	✓	✓		
Record adverse event by investigator		✓	✓	✓	✓	✓ (If dermatitis occurs)	✓ (If dermatitis occurs)
Adverse event by volunteer		✓	✓	✓	✓	✓	✓
Assess patient's quality of life	✓						✓

Data collection

Data collection in the study includes general information and demographic data and the outcome of the study as following:

1. **General information and demographic data**
   - Age
   - Gender
   - Underlying diseases
   - Drug/food allergy
   - Family history of atopic dermatitis
   - Smoking status
   - Hobbies
   - Occupation
   - Current medications
   - Personal care products e.g. cosmetic, dental care products
   - History of dental procedure
   - History of manicure
   - History of food-induced cheilitis rash
   - Other associate symptoms
   - Disease duration and disease severity
   - Frequency of relapse
   - History of prior treatment
   - History of previous patch testing
2. **The outcome of the study**
   - Positive allergens
   - Clinical relevance
   - Adverse event
   - Dermatology life quality index (DLQI) score

Once the data collection from the case record form is completed, all volunteer data will be recorded in the Microsoft Excel program and checked for accuracy. This data will be further analyzed. The complete data files will be stored on the investigators'

personal computer with access protected by a password. After the research is concluded, the data files will be retained for a period of 5 years before being permanently deleted. As for research documents in paper form, they will be stored securely in a locked cabinet with a thick padlock and only the investigators will have access to open it. The documents will be destroyed after the timeframe is completed.

Statistical analysis

Descriptive statistics

The study will involve two types of data: categorical and continuous.

1. **Categorical data** will include information such as occupation, gender, hobbies, underlying disease, family history of atopic dermatitis, and history of prior treatment. These data will be reported in frequency and percentage.

2. **Continuous data** will include variables such as age, weight, height, disease duration, and frequency of a relapse. If the continuous data follow a normal distribution, they will be reported as mean with standard deviation (SD). However, if the continuous data are non-normally distributed, they will be reported as a median and inter-quartile range.

Inferential statistics

To measure the patient's quality of life before and after avoiding the allergens in a patient with allergic contact dermatitis using the Dermatology life quality index (DLQI) will report continuous data in the form of the mean value. Consequently, the mean value between before and after will compare by using a paired-T test.

Research timeline and protocols

1. Research topic, review of related literature, and hypothesis stimulation
2. Research committee, proposal defense, and ethic committee
3. Recruiting participants of online survey
4. Conduct research
5. Analysis of data
6. Presentation and submission for publication of research

Research timelines

The research was conducted between 1 May 2023 and 30 Jun 2025, as detailed in Table 10.

Table 10 Research timelines

	2023		2024												2025		
Research protocols/ months	May-Jun	July-Dec	Jan	Feb	March	April	May	Jun	July	Aug	Sep	Oct	Nov	Dec	Jan- Feb	March-	Jun
Research topic and review	✓																
Proposal	✓																
Ethic committee		✓															
Online survey			✓														
Conduct research			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Data analysis															✓		
Results and discussion																✓	
Presentation and submission																	✓

Research budget

The detailed research budget is presented in Table 11.

Table 11 Research budgets

List	Financial statement (Baht)
1. Compensation	
1.1 Research assistant	4,000.00
1.2 Research participant (150 bath/visit)	72,000.00
2. Material and supplied	
2.1 Patch testing IQ ultimate patch test unit	64,000.00
2.2 Micropore plaster	1,000.00
2.3 Document folder	1,600.00
2.4 Medication if any adverse event occurs	4,000.00
3. Others	
3.1 Document printing	1,500.00
3.2 Telephone bills	200.00
3.3 Utilities cost	1,300.00
Total	**150,000.00 bath**

Chapter 4
Results

The “Clinically Relevant Allergens and Sociodemographic Characteristics in Patients with Allergic Contact Cheilitis: A Cross-Sectional Study” was approved by the Human Research Ethics Committee of Srinakharinwirot University (SWUEC-661022). The researcher divided the data analysis into three stages, as described below:

Part 1: General demographic data of the participants

Part 2: Patch test and DLQI results

Part 3: Adverse events experienced by participants during the research project

Part 1: General demographic data of the participants

Between January 2024 and December 2024, a total of 108 patients were assessed for eligibility to participate in this prospective study on allergic contact cheilitis. Of these, 28 patients were excluded: 12 did not meet the inclusion criteria, and 16 declined to participate.

A total of 80 participants who met the eligibility criteria were enrolled in the study. All participants were at least 18 years of age and had been clinically diagnosed with allergic contact cheilitis. All participants underwent patch testing using 3 allergens series as follows: (1) The SWU Baseline Series (Modified European Baseline Series), (2) Vehicles, Preservatives, and other supplemental allergens Series, (3) Dental and Cheilitis Series, and (4) personal care products (up to 10 products).

All 80 participants completed the patch test readings, allowing comprehensive analysis of the patch test results. Follow-up assessments were conducted on days 14 and 49 to monitor adverse events and assess the DLQI following allergen avoidance. Of the 80 participants, 73 (91.25%) completed all scheduled follow-up visits on days 0, 1, 2, 3, 7, 14, and 49. Seven patients (8.75%) were lost to follow-up due to unwillingness to

continue, with one patient discontinuing on days 14, and six patients on day 49 (Figure 6).

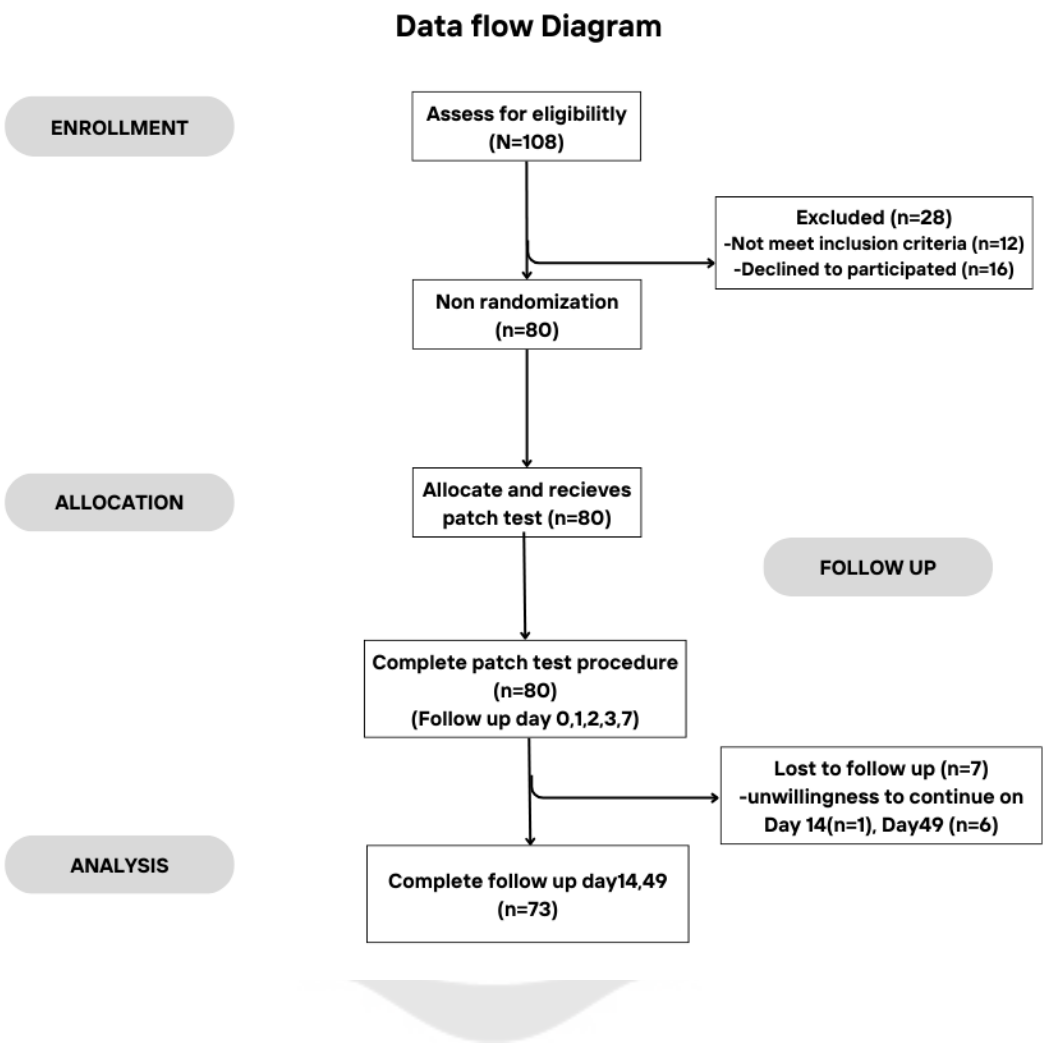

Figure 6 Data flow diagram

The study cohort consisted predominantly of female patients (n = 72), with a mean age of 30.11 years (SD ±6.98). Among the two patients diagnosed with non-allergic contact cheilitis, the mean age was 27.5 years. The mean duration of symptoms was 20.27 months. Thirteen patients (16.67%) reported symptoms duration of less than three months, while 65 patients (83.34%) experienced symptoms for three months or longer. Participants' occupations were distributed as follows: others (n = 32), office workers (n =

20), students (n = 12), healthcare workers (n = 7), administrative staff (n = 5), a chemist (n = 1), and a teacher (n = 1).

Regarding underlying diseases, allergic rhinitis was the most common comorbidity (n = 34, 43.59%), followed by atopic dermatitis (n = 7, 8.97%), asthma (n = 7, 8.97%), and other conditions including gastritis, breast cancer, migraine, polycystic ovary syndrome, dyslipidemia, stroke, and major depressive disorder (n = 9). Additionally, 16 patients reported a family history of atopic diathesis.

In terms of clinical presentation, 31 patients (39.74%) exhibited sole cheilitis, while 47 patients (60.25%) had cheilitis as a primary diagnosis accompanied by dermatitis at other sites. Additional affected areas were most commonly the face (48.94%), followed by the upper extremities (36.17%), lower extremities (34.04%), and neck (31.91%). The trunk was involved in 27.66% of patients, while eyelid involvement was noted in 23.40%. Scalp and hand lesions were each observed in 17.02%, and scattered or generalized involvement was present in 14.89%. Less frequently affected sites included the feet (6.38%) and genital area (2.13%).

The Baseline demographic data and clinical characteristics of the participants are shown in Table 12.

Table 12 Baseline demographic data and clinical characteristics of the participants

Demographic data	Allergic contact cheilitis N=78
Sex, n (%)	
Female	72 (92.30)
Age, Year (Mean ± SD)	30.11 ± 6.98)
Occupation, n (%)	
Others	32 (41.03)
Office worker	20 (25.64)
Student	12 (15.38)
Healthcare worker	7 (8.97)
Administrative	5 (6.41)
Chemist	1 (1.28)
Teacher	1 (1.28)
Mean duration of symptoms, month	20.27
Duration < 3 month, **n (%)**	13 (16.67)
Duration ≥ 3 month, **n (%)**	65 (83.34)
Having an underlying disease n (%)	
U/D -Allergic rhinitis (AR)	34 (43.59)
U/D -Atopic dermatitis (AD)	7 (8.97)
U/D -Asthma	7 (8.97)
U/D- Others	9 (11.54)
Familial history of atopic diathesis	16 (20.51)
Clinical manifestation, n (%)	
Sole cheilitis	31 (39.74)
Cheilitis as a primary diagnosis accompanied by dermatitis at other sites	47 (60.25)

Table 12 Baseline demographic data and clinical characteristics of the participants (continued)

Demographic data	Allergic contact cheilitis N=78
- Scalp	8 (17.02)
- Eyelid	11 (23.40)
- Face	23 (48.94)
- Neck	15 (31.91)
- Upper extremities	17 (36.17)
- Trunk	13 (27.66)
- Genital	1 (2.13)
- Lower extremities	16 (34.04)
- Hand	8 (17.02)
- Foot	3 (6.38)
- Scattered/generalization	7 (14.89)

Part 2: Patch test and DLQI results

2.1 Overall Positive Patch Test Reactions

Regarding patch test results in this ACC cohorts, 68 out of 78 patients (87.18%) had at least one positive reaction to the SWU Baseline Series, of which 65 cases showed clinical relevance. There were 3 patients with doubtful reactions that showed clinical relevance, i.e. (1) hydroperoxides of linalool in one case which linalool was found in the toothpaste, (2) fragrance mix II in skin care products, and (3) propolis, fragrance mix II, and sorbitan sesquioleate in Sparkle toothpaste.

Fifty-eight patients out of 78 (73.10%) had at least one positive reaction to our dental and cheilitis series with clinical relevance in 31 patients. Four patients with doubtful reactions were called clinical relevance with the following allergens: vanillin (N = 3), carvone (N = 2), benzyl alcohol (N = 1), and diallyl disulfide (N = 1).

For our preservative and vehicle series, 52 out of 78 patients (66.67%) had at least one positive reaction, 43 patients showed clinical relevance. In addition, 8 cases with doubtful reactions showed clinical relevance with the following allergens: cocamidopropyl betaine (N = 4), gallate mix (N = 4), sodium benzoate (N = 2). These allergens were found in lipsticks, toothpaste, and facial cleanser.

Among the 78 patients with allergic contact cheilitis, the most frequent positive patch test reactions were found in hydroperoxides of linalool (n = 28, 35.90%), gallate mix (n = 26, 33.33%), benzisothiazolinone (n = 22, 28.21%), nickel sulfate (n = 21, 26.92%), gold sodium thiosulfate (n = 19, 24.36%), sodium tetrachloropalladate (II) hydrate (n = 19, 24.36%), benzalkonium chloride (n = 19, 24.36%), palladium chloride (n = 17, 21.79%), potassium dichromate (n = 16, 20.51%), and copper sulfate (n = 16, 20.51%). %). Details of positive patch test reactions are shown in Table 13

An additional twelve positive reactions were identified on Day 7 reading. These included two reactions to formaldehyde and two to palladium chloride, as well as one reaction each to budesonide, carba mix, copper sulfate, decyl glucoside, glutaraldehyde, imidazolidinyl urea, lanolin, and methylisothiazolinone. All additional reactions were graded as 1+.

Table 13 Positive patch test reactions among 78 patients with allergic contact cheilitis in our cohort (by frequency of positive reactions)

Allergens	Test Conc. (%)	Reactions on 72-hour reading					N positive (%)
		?	+	++	+++	IR	
Hydroperoxides of Linalool	1.0% pet.	6	25	3	0	0	28 (35.90)
Gallate mix	1.0% pet.	26	20	6	0	3	26 (33.33)
Benzisothiazolinone	0.1% pet.	13	21	1	0	0	22 (28.21)
Nickel sulfate	5.0% pet.	2	11	3	7	0	21 (26.92)
Gold sodium thiosulfate	0.5% pet.	10	12	3	4	0	19 (24.36)
Sodium tetrachloropalladate(II)hydrate	3.0% pet.	7	15	3	1	0	19 (24.36)
Benzalkonium chloride	0.1% aq.	10	13	6	0	7	19 (24.36)
Palladium chloride	2.0% pet.	11	14	3	0	0	17 (21.79)
Potassium dichromate	0.5% pet.	16	16	0	0	0	16 (20.51)
Copper sulfate	2.0% pet.	9	15	1	0	0	16 (20.51)
Mercury	0.5% pet.	7	15	1	0	0	16 (20.51)
Cobalt chloride	1.0% pet.	13	12	3	0	0	15 (19.23)
Sodium benzoate	5.0% pet.	14	10	4	0	0	14 (17.95)
Propylene glycol	30.0% pet.	*3*	*12*	*2*	*0*	*0*	14 (17.95)
Hydroperoxides of Limonene	0.3% pet.	3	11	2	0	0	13 (16.67)
Carba mix	3.0% pet.	5	12	1	0	0	13 (16.67)
Myroxylon pereirae	25.0% pet.	2	9	2	1	0	12 (15.38)
Paraben mix	16.0% pet.	5	9	1	0	0	10 (12.82)
Methylisothiazolinone	0.20% aq.	14	10	0	0	0	10 (12.82)
Lanolin (wool alcohols)	30.0% pet.	6	9	0	0	0	9 (11.54)
Textile dye mix	6.6% pet.	28	8	1	0	0	9 (11.54)
Fragrance mix I	8.0% pet.	2	7	0	1	0	8 (10.26)
Methyldibromo glutaronitrile	0.5% pet.	7	8	0	0	0	8 (10.26)
Neomycin sulfate	20.0% pet.	2	7	0	0	0	7 (8.97)
Decyl glucoside	5.0% pet.	3	7	0	0	0	7 (8.97)
Benzyl alcohol	10.0% pet.	4	7	0	0	0	7 (8.97)
Castor oil	100.0%	6	4	2	1	0	7 (8.97)
Tocopherol	100.0% pet	0	7	0	0	0	7 (8.97)
Colophonium	20.0% pet.	3	3	1	2	0	6 (7.69)

Table 13 Positive patch test reactions among 78 patients with allergic contact cheilitis in our cohort (by frequency of positive reactions) (continued)

Allergens	Test Conc. (%)	Reactions on 72-hour reading					N positive (%)
		?	+	++	+++	IR	
MCI/MI	0.02% aq.	3	6	0	0	0	6 (7.69)
Sorbitan sesquioleate	20.0% pet.	5	6	0	0	0	6 (7.69)
Sorbitan monooleate	5.0% pet.	5	6	0	0	0	6 (7.69)
Aluminium(III)chloride	2.0% pet.	18	6	0	0	0	6 (7.69)
4-tert-Butylphenol formaldehyde resin	1.0% pet.	1	5	0	0	0	5 (6.41)
Sesquiterpene lactone mix	0.1 pet.	1	5	0	0	0	5 (6.41)
Propolis	10.0% pet.	9	4	1	0	0	5 (6.41)
Eugenol	2.0% pet.	3	5	0	0	0	5 (6.41)
Carvone	5.0% pet.	5	5	0	0	0	5 (6.41)
Cocamidopropyl betaine	1.0% pet.	9	5	0	0	6	5 (6.41)
Hexyl cinnamic aldehyde	10.0% pet.	5	3	1	0	0	4 (5.13)
p-Phenylenediamine	1.0% pet.	2	1	2	0	0	3 (3.85)
Formaldehyde	2.0% aq.	2	3	0	0	0	3 (3.85)
Fragrance mix II	14.0% pet.	5	2	1	0	0	3 (3.85)
Glutaraldehyde	0.5% pet.	2	3	0	0	0	3 (3.85)
Methyl methacrylate	2.0% pet.	2	3	0	0	0	3 (3.85)
Caine mix	10.0% pet.	1	2	0	0	0	2 (2.56)
Epoxy resin, Bisphenol A	1.0% pet.	2	2	0	0	0	2 (2.56)
Budesonide	0.01% pet.	0	2	0	0	0	2 (2.56)
2-Bromo-2-nitropropane-1,3-diol	0.5% pet.	2	2	0	0	0	2 (2.56)
Diazolidinyl urea	2.0% pet.	1	2	0	0	0	2 (2.56)
2-n-Octyl-4-isothiazolin-3-one	0.1% pet.	5	2	0	0	0	2 (2.56)
Compositae mix II	5.0% pet.	0	1	1	0	0	2 (2.56)
Mentha piperita oil	2.0% pet.	4	2	0	0	0	2 (2.56)
Imidazolidinylurea	2.0% pet.	1	2	0	0	0	2 (2.56)
2-Hydroxyethyl methacrylate	2.0% pet.	0	0	1	0	0	1 (1.28)
N-Isopropyl-N'-phenyl-p-phenylenediamine	0.1% pet.	1	1	0	0	0	1 (1.28)
Mercapto mix	2.0% pet.	1	0	1	0	0	1 (1.28)
Sodium metabisulfite	1.0% pet.	1	0	1	0	0	1 (1.28)
Vanillin	10.0% pet.	6	0	1	0	0	1 (1.28)
2-Phenoxyethanol	1.0% pet.	0	1	0	0	0	1 (1.28)

MCI/MI, Miethylchloroisothiazolinone/Methylisothiazolinone;

2.2 Clinically relevant patch test reactions in the patient with allergic contact cheilitis

Clinical relevance was assessed in all cases by correlating the sensitization with patient history, dermatitis localization, and known allergen exposures. Relevance was classified as definite, probable, or possible, based on the strength of the association between the allergens and the patient's clinical presentation. This evaluation was conducted using the Standardized Patch Test Relevance Index (SPIN) (Table 14)

Table 14 Clinically relevant patch test results in the patient with allergic contact cheilitis and SPIN analysis.

Allergens	Test Conc. (%)	N of Clinical Relevance			N positive (%)	SPIN
		Definite	Probable	Possible		
Hydroperoxides of Linalool	1.0% pet	5	9	14	28/28 (100%)	5585.64
Gallate mix	1.0% pet	2	6	1	9/26 (34.6%)	2096.67
Sodium benzoate	5.0% pet	4	8	0	12/14 (85.7%)	1665.64
Propylene glycol	30.0% pet	1	12	0	13/14 (92.8%)	1601.03
Myroxylon pereirae	25.0% pet	1	11	0	12/12 (100%)	1270.77
Hydroperoxides of Limonene	0.3% pet	2	6	5	13/13 (100%)	1268.33
Fragrance mix I	8.0% pet	1	7	0	8/8 (100%)	576.41
Tocopherol	100% pet	4	3	0	7/7 (100%)	536.67
Castor oil	i100.0%	1	5	1	7/7 (100%)	415.51
Sorbitan sesquioleate	20.0% pet	3	3	0	6/6 (100%)	383.08
Sorbitan monooleate	5.0% pet	3	3	0	6/6 (100%)	383.08
Benzyl alcohol	10.0% pet	1	4	0	5/7 (71.4%)	326.67
Paraben mix	16.0% pet	1	2	0	3/10 (30%)	297.44
Lanolin (wool alcohols)	30.0% pet	0	3	1	4/9 (44.5%)	266.54
Nickel sulfate	5.0% pet	0	1	0	1/21 (4.8%)	177.69
Eugenol	2.0% pet	1	0	4	5/5 (100%)	148.72
Propolis	10% pet	0	3	1	4/5 (80%)	148.08
Cocamidopropyl betaine	1.0% pet	0	3	0	3/5 (60%)	126.92
Sesquiterpene lactone mix	0.1% pet	0	0	5	5/5 (100%)	105.77
Carvone	5.0% pet	0	0	5	5/5 (100%)	105.77
Fragrance mix II	14.0% pet	2	1	0	3/3 (100%)	102.31
Benzisothiazolinone	0.1% pet	0	0	1	1/22 (4.5%)	93.08
Hexyl cinnamic aldehyde	10.0% pet	0	1	0	1/10 (10%)	84.62

Table 14 Clinically relevant patch test results in the patient with allergic contact cheilitis and SPIN analysis. (continued)

Allergens	Test Conc. (%)	N of Clinical Relevance			N positive (%)	SPIN
		Definite	Probable	Possible		
Benzalkonium chloride	0.1% aq	0	1	3	4/4 (100%)	84.62
Methylisothiazolinone	0.20 aq	0	0	1	1/19 (5.3%)	80.38
Cobalt chloride	1.0% pet	0	0	1	1/15 (6.7%)	63.46
p-Phenylenediamine	1.0% pet	0	1	0	1/7 (14.3%)	59.23
Mentha piperita oil (Peppermint oil)	2.0% pet	0	2	0	2/3 (66.7%)	50.77
2-Hydroxyethyl methacrylate	2.0% pet	0	1	1	2/2 (100%)	25.38
Compositae mix II	5.0% pet	0	1	0	1/2 (50%)	16.92
2-Phenoxyethanol	1.0% pet	0	1	0	1/1 (100%)	8.46
Vanillin	10.0% pet	0	0	1	1/2 (50%)	8.46
Potassium dichromate	0.5% pet	0	1	0	1/1 (100%)	8.46
Thiuram mix	1.0% pet	0	0	1	1/1 (100%)	4.23
Neomycin sulfate	20.0% pet	0	0	0	0/16 (0%)	0
Caine mix	10.0% pet	0	0	0	0/0	0
Colophonium	20.0% pet	0	0	0	0/7 (0%)	0
N-Isopropyl-N'-phenyl-p-phenylenediamine	0.1% pet	0	0	0	0/2 (0%)	0
Mercapto mix	2.0% pet	0	0	0	0/6 (0%)	0
Epoxy resin, Bisphenol A	1.0% pet	0	0	0	0/1 (0%)	0
4-tert-Butylphenol formaldehyde resin	1.0% pet	0	0	0	0/1 (0%)	0
2-Mercaptobenzothiazole	2.0% pet	0	0	0	0/2 (0%)	0
Formaldehyde	2.0% aq	0	0	0	0/5 (0%)	0
Sodium metabisulfite	1.0% pet	0	0	0	0/0	0
MCI/MI	0.02% aq	0	0	0	0/3 (0%)	0
Budesonide	0.01% pet	0	0	0	0/1 (0%)	0
Tixocortol pivalate	0.1% pet	0	0	0	0/6 (0%)	0
Methyldibromo glutaronitrile	0.5% pet	0	0	0	0/0	0
Textile dye mix	6.6% pet	0	0	0	0/8 (0%)	0
Decyl glucoside	5.0% pet	0	0	0	0/9 (0%)	0
2-Bromo-2-nitropropane-1,3-diol (Bronopol)	0.5% pet	0	0	0	0/2 (0%)	0
Diazolidinyl urea	2.0% pet	0	0	0	0/2 (0%)	0
2-n-Octyl-4-isothiazolin-3-one	0.1% pet	0	0	0	0/2 (0%)	0
Carba mix	3.0% pet	0	0	0	0/13 (0%)	0
Glutaraldehyde	0.5% pet	0	0	0	0/3 (0%)	0
Diallyl disulfide	1.0% pet	0	0	0	0/0	0

Table 14 Clinically relevant patch test results in the patient with allergic contact cheilitis and SPIN analysis. (continued)

Allergens	Test Conc. (%)	N of Clinical Relevance			N positive (%)	SPIN
		Definite	Probable	Possible		
BIS-GMA	2.0% pet	0	0	0	0/0	0
BIS-EMA	2.0% pet	0	0	0	0/0	0
Methyl methacrylate	2.0% pet	0	0	0	0/3 (0%)	0
Gold sodium thiosulfate	0.5% pet	0	0	0	0/19 (0%)	0
Copper sulfate	2.0% pet	0	0	0	0/16 (0%)	0
Palladium chloride	2.0% pet	0	0	0	0/17 (0%)	0
Sodium tetrachloropalladate(II)hydrate	3.0% pet	0	0	0	0/19 (0%)	0
Mercury	0.5% pet	0	0	0	0/16 (0%)	0
Imidazolidinylurea (Germall 115)	2.0% pet	0	0	0	0/2 (0%)	0
Quaternium-15	1.0 % pet	0	0	0	0/0	0
Aluminium(III)chloride	2.0% pet	0	0	0	0/6 (0%)	0
DMDM hydantoin	1.0% pet	0	0	0	0/0	0

MCI/MI, Miethylchloroisothiazolinone/Methylisothiazolinone;
BIS-GMA, 2,2-bis(4-(2-Hydroxy-3-methacryloxypropoxy)phenyl)propane;
BIS-EMA, 2,2-bis(4-(2-Methacryl-oxyethoxy)phenyl)propane

To provide further clarity, the top ten clinically relevant allergens were identified, encompassing two major categories: (1) fragrance-related allergens (hydroperoxides of linalool, *Myroxylon Pereirae,* hydroperoxides of limonene, and fragrance mix I) and (2) preservatives and cosmetic-related allergens (sodium benzoate, propylene glycol, tocopherol, castor oil, sorbitan sesquioleate, and sorbitan oleate. Lip makeup and toothpaste were the most common sources of allergen exposure. Detailed key sources and product types were demonstrated in Table 15.

The most clinically relevant allergen, hydroperoxides of linalool, 3 showed the highest SPIN score indicating a strong association with ACC. Possibly from the oxidation process of linalool in the skincare products. It was found in lip products (7 patients), fragranced toothpaste (4 patients), and skincare items (17 patients).

Followed by gallate mix, 34.62% of positive patch test deemed clinically relevant, i.e., 2 definite, 6 probable, and 1 possible. Gallates are used as preservatives and antioxidants. The relevance of gallates was observed primarily in lip products containing propyl gallate, affecting 9 patients in total.

Sodium benzoate accounted for 14 positive reactions, 12 of which were clinically relevant, including 4 definite cases. With a SPIN score of 1665.64, its relevance was especially notable in toothpaste (5 patients), cleansing products (3 patients), lip products (1 patient), and moisturizers (3 patients). Although commonly used as a preservative, sodium benzoate can provoke allergic responses in susceptible individuals.

Similarly, propylene glycol demonstrated substantial clinical relevance, with 14 positive reactions, 13 of which were clinically relevant (1 definite). This allergen yielded a SPIN score of 1601.03 and was implicated in lip products (3 patients), toothpaste (3 patients), cleansing products (4 patients), and skincare products (3 patients). Its role as a humectant and solvent underscores its widespread presence in personal care formulations.

Continuing with fragrance-related allergens, *Myroxylon Pereirae* showed 12 positive reactions, with 11 classified as probable clinical relevance and a SPIN score of 1270.77. The allergen is found in fragranced skincare products and toothpaste used by all 12 affected patients.

In addition, hydroperoxides of limonene resulted in 13 clinically relevant reactions, including 2 definite cases, and a SPIN score of 1268.33. Clinical associations were identified primarily in fragranced products such as lipstick (5 patients), skincare (6 patients), and toothpaste (2 patients). The oxidized derivatives of limonene are known to be more allergenic than the unoxidized compound.

Fragrance mix I also contributed to 8 clinical relevant reactions (7 probable) with a SPIN score of 576.41, predominantly from fragranced skincare and toothpaste products.

Regarding antioxidants, tocopherol showed 7 clinically relevant reactions, including 4 definite cases, with a SPIN score of 536.67. Exposure was primarily via lip products (6 patients) and vitamin E-based products (1 patient).

Castor oil demonstrated relevance in 7 patients, with 1 definite and 6 probable reactions, yielding a SPIN score of 445.13. The allergen was present in lip products (1 patient), moisturizers (5 patients), and one dental product.

Finally, both sorbitan sesquioleate and sorbitan monooleate exhibited 6 positive reactions each, with 3 classified as clinically relevant for both allergens. Each yielded a SPIN score of 383.08, with toothpaste identified as the primary source of exposure.

Table 15 Top 10 clinically relevant allergens in allergic contact cheilitis with key sources

Rank	Allergen	SPIN Score	Clinically Relevant Reactions (%)	Key Sources / Product Types (number of patients)
1	Hydroperoxides of Linalool	5586	28/28 (100%)	Skincare (17), Lip makeup (7), toothpaste (4)
2	Gallate mix	2097	9/26 (34.62%)	Lip makeup (9)
3	Sodium benzoate	1666	12/14 (85.71%)	Toothpaste (5), cleanser (3), Lip makeup (1), moisturizers (3)
4	Propylene glycol	1601	13/14 (92.86%)	Lip makeup (3), toothpaste (3), cleanser (4), skincare (3)
5	*Myroxylon pereirae*	1271	12/12 (100%)	Fragranced skincare/toothpaste (12)
6	Hydroperoxides of Limonene	1268	13/13 (100%)	Lip makeup (5), fragranced skincare (6), toothpaste (2)
7	Fragrance mix I	576.4	8/8 (100%)	Toothpaste/skincare (8)
8	Tocopherol	536.7	7/7 (100%)	Lip makeup (6), vitamin E skincare (1)
9	Castor oil	445.1	7/7 (100%)	Lip makeup (1), moisturizer (5) , Dental floss (1)
10	Sorbitan sesquioleate and Sorbitan oleate	383.08 each	6/6 each (100%)	Toothpaste (6)

2.3 Personal Product Testing

In the analysis of patient-reported personal products and their association with allergic reactions, a total of 382 products were tested across various categories. The overall percentage of positive reactions was 14.92% (57 out of 382 products) (Table 16). Product categories associated with positive reaction were ranked from highest to lowest as follows: lip products (8.64%), toothpaste (4.18%), moisturizer (1.83%), and make-up (0.26%).

Table 16 Personal product testing results

Personal Products	No. of products	No. of positive reaction	No. (%) of positive reaction in each product category
Lip product	201	33	33/201 (16.41)
- Lipstick	124	20	20/124 (16.12)
- Lip Balm/oil	77	13	13/77 (16.88)
Toothpaste	116	16	16/116 (13.79)
- Toothpaste (50% pet)	58	3	3/58 (5.17)
- Toothpaste (as is)	58	13	13/58 (22.41)
Others product	65	8	8/65 (12.30)
- Moisturizer	40	7	7/40 (17.50)
- Make up for skin	8	1	1/8 (12.50)
- Sunscreen	10	0	0/10 (0)
- Cleansing product	3	0	0/3 (0)
- Hair care product	2	0	0/2 (0)
- Medication	2	0	0/2 (0)

2.4 Dermatology life quality Index (DLQI) grading result

The dermatology life quality index (DLQI) was used to assess the impact of allergic contact cheilitis on patients' quality of life. The questionnaire was administered at Day 0 before patch testing and again at Day 49 after the patch testing procedure.

At Day 0, the mean DLQI score was 10.10, indicating a moderate to severe impact on patients' quality of life due to the symptoms of allergic contact cheilitis. This result reflects the common challenges faced by patients, including physical discomfort, emotional distress, and social limitations associated with the condition. (Figure 7)

By Day 49, following patch testing and allergen avoidance, the mean DLQI score significantly improved to 2.416, demonstrating a marked reduction in the impact of the condition on patients' daily lives. This improvement suggests that the patch testing process, combined with allergen identification and avoidance, was effective in reducing the symptoms and improving the overall well-being of patients with allergic contact cheilitis.

This significant decrease in the DLQI score highlights the importance of accurate diagnosis and allergen management in improving the quality of life for individuals suffering from allergic contact cheilitis.

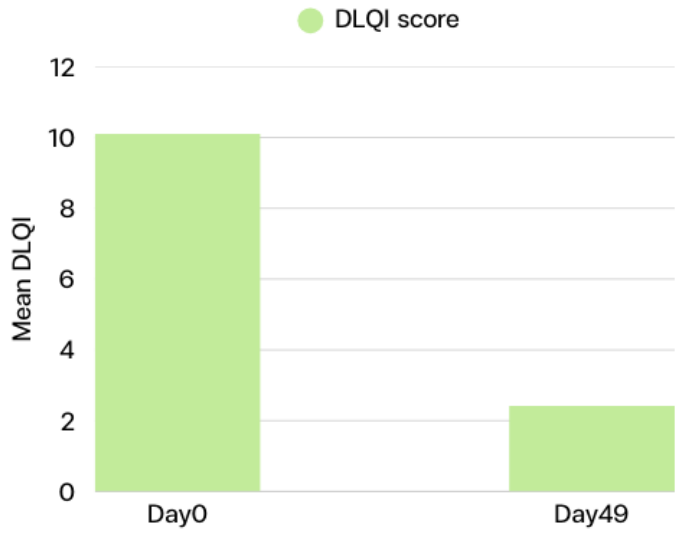

Figure 7 Dermatology life quality index (DLQI) assessed at baseline (Day 0) and following allergen avoidance (Day 49)

Part 3 Adverse events experienced by participants during the research project.

3.1 Erythema

Erythema was assessed on Day 14 and Day 49 using a grading scale from 0 (no erythema) to 4 (marked erythema). On Day 14, the majority of patients (61, 78.2%) showed no erythema (grade 0). Barely noticeable erythema (grade 1) was observed in 12 patients (15.4%), all of which were attributed to tape reactions rather than positive patch test reaction. Mild erythema (grade 2) was present in 6 patients (7.7%), with 4 of these occurring at the patch test site: three participants showed mild erythema at the gold test site and one at the copper sulfate site. By Day 49, 62 patients (79.5%) continued to show no erythema, while barely noticeable erythema was seen in 8 patients (10.3%). Mild erythema persisted in 3 patients (3.8%), including one patient who had a persistent positive mild erythema reaction at the gold test site and two patients with tape reaction-related erythema. (Figure 8) These results indicate that erythema as a side effect of patch testing was generally minimal and transient, with only a few cases of persistent mild erythema localized to the gold allergen site.

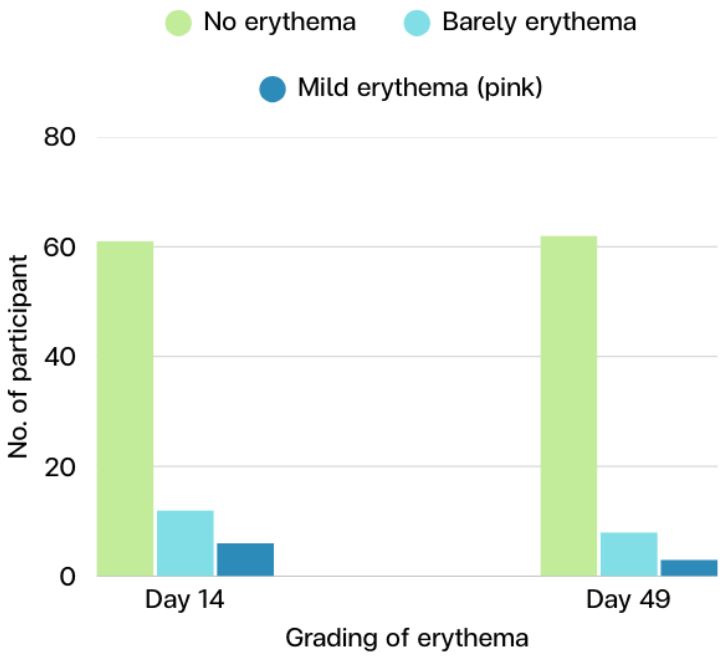

Figure 8 Grading of erythema on day 14 and 49

3.2 Post-inflammatory hyperpigmentation

Post-inflammatory hyperpigmentation (PIH) was assessed on Day 14 and Day 49. On Day 14, 29 patients (37.18%) showed no hyperpigmentation, while 12 patients (15.38%) had barely noticeable hyperpigmentation. Mild hyperpigmentation was observed in 21 patients (26.92%), moderate hyperpigmentation in 16 patients (20.51%) and severe hyperpigmentation was rare, occurring in only 1 patient (1.28%).

By Day 49, 35 patients (44.87%) showed no hyperpigmentation. While barely noticeable and mild hyperpigmentation were observed in 18 patients (23.08%) and 17 patients (21.79%), respectively. Only 2 patients (2.56%) had moderate hyperpigmentation, and 1 patient (1.28%) showed severe hyperpigmentation. These findings indicate that the majority of PIH cases were mild to moderate and showed improvement over the course of the study. (Figure 9)

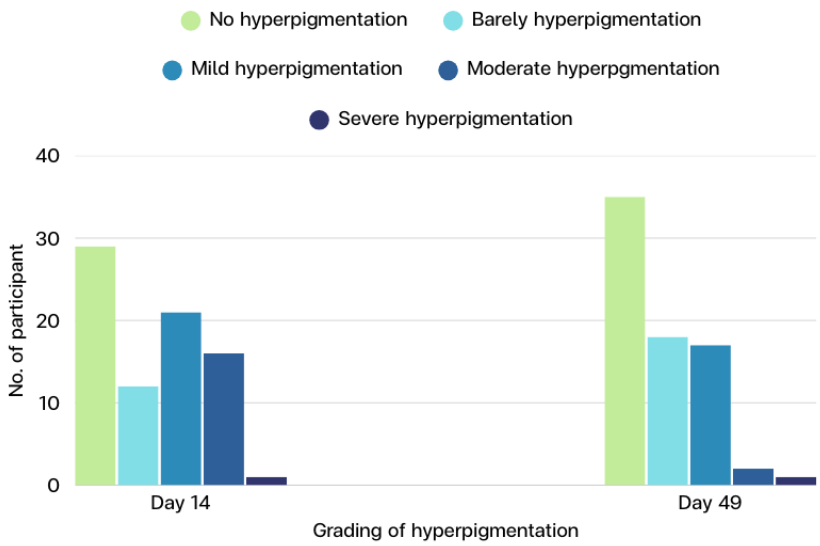

Figure 9 Grading of hyperpigmentation on day 14 and 49

3.3 Dermatitis flare-up

Dermatitis flare-ups following patch testing were observed in a small subset of patients. On Day 14, 5 patients (6.4%) experienced flare-ups, while the majority, 74 patients (94.9%), showed no exacerbation. By Day 49, flare-ups had further decreased, with only 3 patients (3.8%) affected, and 70 patients (89.7%) remaining free of flare-ups. These results indicate that dermatitis flare-ups after patch testing were uncommon and generally improved over time.

On Day 14, flare-ups included lip dermatitis in 2 participants and trunk dermatitis in 3 participants. By Day 49, flare-ups were present in 1 participant with lip dermatitis and 2 participants with trunk dermatitis. Notably, one participant experienced intermittent trunk dermatitis flare-ups from Day 14 through Day 49 and required treatment with topical steroids, antihistamines, and oral steroids. The remaining patients experienced spontaneous resolution without treatment following allergen avoidance. Overall, the low incidence and resolution of flare-ups support the safety of patch testing in patients with allergic contact cheilitis. (Figure 10)

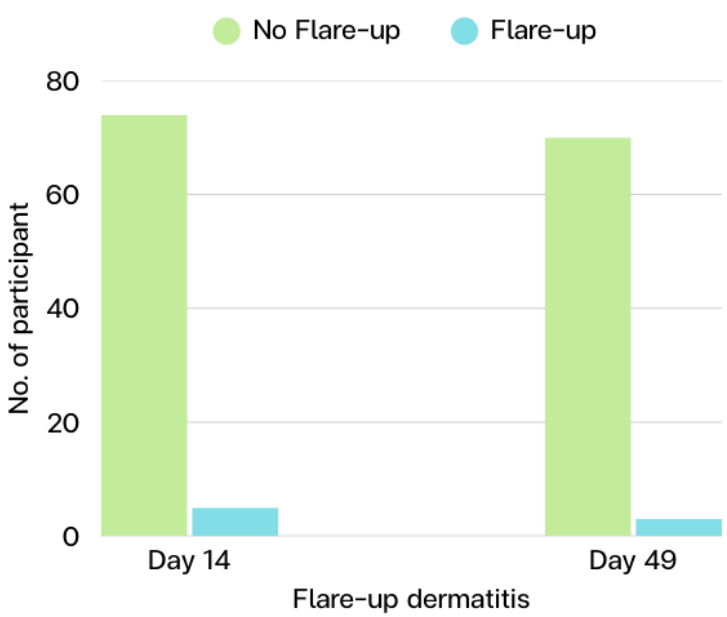

Figure 10 Flare-up dermatitis assessment on day 14 and 49

3.4 Pruritus

Pruritus at patch site test was assessed using the Visual Analog Scale (VAS) (0-10 score) across five time points: Day 2, Day 3, Day 7, Day 14, and Day 49.

On Day 2, the mean VAS score was 5.83, indicating moderate itching in many patients. The intensity remained high on Day 3 with a mean score of 5.41, reflecting persistent pruritus. By Day 7, the mean VAS score dropped to 2.15, suggesting a decrease in the intensity of itching.

On Day 14, the mean score further decreased to 1.15, and by Day 49, the score significantly dropped to 0.64, indicating a marked reduction in pruritus over time. These results suggest that pruritus was most intense in the initial days post-test but subsided significantly within the study period. (Figure11)

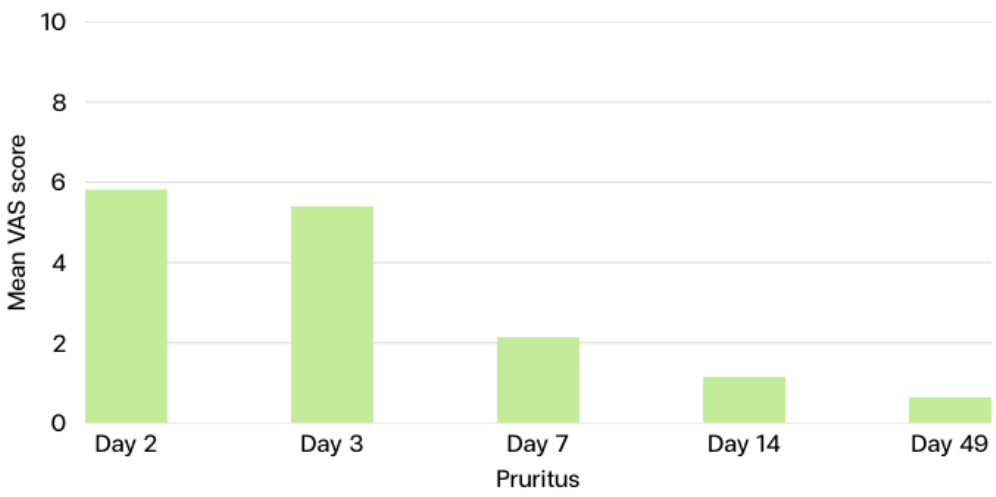

Figure 11 Mean VAS score of pruritus assessment on day 2, 3, 7, 14,and 49

Chapter 5
Discussion

5.1. Demographics

This study involved 78 patients diagnosed with Allergic Contact Cheilitis (ACC) in Thailand, with a predominance of females (92.30%) and a mean age of 30.11 years (SD 6.98). This gender distribution aligns with findings from Silverberg et al [(39)] whom reported a higher prevalence of cheilitis among females, likely attributed to greater exposure to cosmetics and personal care products. Freeman and Stephens[(23)] further noted that 67% of their Australian cohort were female, reinforcing the association between female gender and increased risk of cheilitis due to frequent allergen exposure in personal care products.

Regarding occupation, no participants reported a direct clinical relationship between their work environment and cheilitis onset or exacerbation. Similarly, dental procedures such as tooth scaling, fillings, dental crowns, braces, teeth whitening, and nail treatments including gel or acrylic nails were not reported by participants as contributing factors to their condition.

In terms of comorbidities, allergic rhinitis (43.59%) and atopic dermatitis (8.97%) were the most prevalent, paralleling findings from Silverberg et al [(41)] and Kanokrungsee et al. [(40)], which highlight the increased susceptibility of atopic individuals to contact dermatitis due to heightened immune sensitivity. Additionally, 16 patients (20.51%) reported a family history of atopic diseases, supporting the notion of a genetic predisposition to cheilitis and related allergic conditions. The genetics of contact allergy remain only partly understood, but evidence suggests that polymorphisms in candidate genes such as NAT1, NAT2, GSTM, GSTT, ACE, TNF, and IL-16 are associated with an increased risk of contact allergy, particularly in polysensitized individuals. [(72)]These findings highlight a possible overlap between inherited susceptibility and environmental exposures in the pathogenesis of allergic contact cheilitis.

5.1. Patch test results

Analysis of our patient cohort revealed significant rates of positive patch test reactions with established clinical relevance for several allergens. The highest prevalence of sensitization was observed for hydroperoxides of linalool (35.90%), gallate mix (33.33%), and sodium benzoate (17.95%). The clinical impact of these allergens was underscored by their respective SPIN scores of 5585.64, 2096.67, and 1665.64. Other frequently observed relevant allergens within the top ten included propylene glycol, *Myroxylon pereirae* resin, hydroperoxides of limonene, fragrance mix I, tocopherol, castor oil, and sorbitan sesquioleate.

These findings closely align with the results of the retrospective study by O'Gorman and Torgerson [11] , conducted in the United States between 2001 and 2011, where nearly half of the patients with non-actinic cheilitis were diagnosed with allergic contact cheilitis. In their study, key allergens included Fragrance mix (26.8%), *Myroxylon pereirae* resin (24.4%), dodecyl gallate (19.5%), octyl gallate (14.6%). The similarity in results highlights the persistent role of fragrances, antioxidants (gallates), as primary sensitizers across different populations.

Hydroperoxides of linalool, a potent oxidized fragrance allergen, was the most clinically relevant allergen in our cohort. While linalool itself has a low sensitization potential, its oxidation products—Hydroperoxides of linalool—are strong sensitizers commonly found in fragranced cosmetic products. In our cohort, 5 patients showed definite clinical relevance due to positive personal product tests containing linalool, 9 patients showed probable clinical relevance from personal products containing linalool that were not tested, and 14 patients showed possible clinical relevance from fragrance-containing cosmetic products. In the U.K. [73], products containing fragrance are most commonly found in personal care items, household products, and cosmetics, with linalool and limonene being the most frequently encountered fragrances. This highlights the significant role these allergens play in allergic contact cheilitis. The increasing prevalence of positive reactions to oxidized compounds, as reported by Sukakul et al [74], is especially noticeable in regions with high fragrance product use. This global trend is reflected in our

cohort, with rising sensitization observed in both Asian and European populations, likely driven by the growing use of fragranced personal care products and improvement in patch test detection methods.

Gallates, particularly propyl Gallate, are significant allergens commonly found in cosmetics such as lipsticks and sunscreens, where they serve as antioxidants and preservatives. The sensitization potential of gallates increases with the length of the alkyl side chain, with dodecyl gallate being the strongest sensitizer, followed by octyl gallate and propyl gallate. In our cohort, gallate mix was the second most prevalent allergen, with 33.33% of patients testing positive, underscoring the role of propyl gallate in cosmetic-induced allergic contact cheilitis. Among those who tested positive, 2 patients had definite clinical relevance and 6 had probable clinical relevance, particularly from lip products containing propyl gallate.

These findings align with Garcia et al[75], who found cheilitis as the most common presentation (63%) among 46 patients sensitized to gallates, with lipstick (54.3%) as the primary sensitizing agent. The study underscores the need for patch testing to identify gallates as allergens, particularly propyl Gallate, and emphasizes the importance of allergen avoidance, especially in patients with cosmetic-induced cheilitis.

Sodium benzoate, a preservative widely used in food and cosmetic products, showed significant clinical relevance in our cohort, with 17.95% of patients testing positive. Moreover, Kanokrungsee et al.[40] reported an 8.4% positivity rate in a Thai population.

In contrast, the large multicentre Information Network of Departments of Dermatology (IVDK) study from Germany, Switzerland, and Austria (1996–2009) [76]reported a much lower overall prevalence of 0.69% (0.89% in men, 0.58% in women). Although previously considered a relatively uncommon allergen, the IVDK analysis demonstrated a significant upward trend over time (odds ratio 1.19 per 2 years), indicating that sensitization is becoming more frequent. The markedly higher prevalence in our cohort compared with both Thai and European reports may be attributable to this increasing global trend, as well as differences in patient selection, or regional exposure

patterns—particularly from widespread use in processed foods, beverages, and cosmetic formulations.

Benzisothiazolinone demonstrated positive reactions in a significant portion of our cohort, with prevalences of 28.21% (n = 22). Co-sensitization was notably observed in 17 patients who showed sensitivity to methylisothiazolinone, and 6 patients to Methylchloroisothiazolinone/Methylisothiazolinone mixture (MCI/MI). Co-sensitization between benzisothiazolinone and methylisothiazolinone is well-documented in the literature[77], likely from a shared chemical structures. Patients who are sensitized to one of these chemicals often develop hypersensitivity to the other. In a study by Aalto-Korte et al. [77], benzisothiazolinone-positive patients showed concomitant MI reactions in 33% of cases. Given the widespread use of isothiazolinones in both personal care and household products, making it crucial for clinicians to consider if this allergen relevance when diagnosing allergic contact cheilitis.

The high positive rate of nickel sulfate (26.92%) in our cohort aligns with findings from Silverberg et al. [39], who identified nickel as a leading cause of contact cheilitis. This prevalence highlights the need to consider nickel sulfate in the differential diagnosis of allergic contact cheilitis, particularly in individuals frequently exposed to jewelry, dental materials, and coins.

In addition, Zeng et al. [78]reported the first pediatric case of allergic contact cheilitis caused by nickel released from stainless steel crowns in primary molars, even without direct lip contact. In this case, nickel ions were likely transferred to the lips via saliva, leading to persistent cheilitis that resolved completely after replacing the crowns with resin restorations. This case illustrates that nickel-induced cheilitis can result not only from direct exposure through contaminated cosmetics or jewelry but also from indirect intraoral sources, underscoring the diverse exposure pathways that must be considered in clinical assessment and prevention strategies.

Beyond environmental and occupational exposures, cosmetic products, particularly lipsticks, have been identified as significant sources of nickel contamination. Research has shown that some cosmetic products, especially liquid lipsticks and lip

pencils, contain elevated levels of nickel, with liquid lipsticks containing almost double the concentration found in solid lipsticks. Additionally, high concentrations of nickel were notably present in lip and eye makeup products [79]. Such contamination in cosmetics underscores the potential for allergic reactions, especially in individuals with pre-existing sensitivities.

These findings highlight the need for stringent regulations and consistent monitoring of heavy metal contamination in cosmetics to minimize exposure and protect consumer health. Nickel, being a well-established skin sensitizer, can cause significant adverse effects when present in products applied to sensitive areas like the lips.

Conclusion

This study underscores the clinical significance of specific allergens in the pathogenesis of allergic contact cheilitis (ACC), with hydroperoxides of linalool, gallate mix, and sodium benzoate emerging as the most relevant sensitizers based on both prevalence and SPIN scores. The prominence of fragrance-related allergens and cosmetic preservatives, particularly those found in lip products and personal care items, highlights the pivotal role of daily consumer exposures in eliciting allergic responses. Our findings are consistent with existing literatures, reaffirming the global relevance of these allergens and the rising sensitization trends linked to fragranced products.

Moreover, the observed co-sensitization between benzisothiazolinone and other isothiazolinones, along with the high prevalence of nickel sulfate sensitization, points to the complexity of allergen interactions and the importance of comprehensive patch testing. The detection of nickel contamination in cosmetic products further emphasizes the necessity of stricter regulatory oversight and product safety monitoring.

In clinical practice, these findings advocate for a heightened awareness of cosmetic and preservative allergens when evaluating patients with cheilitis. Identifying and eliminating exposure to relevant allergens remains central to effective management. Ultimately, this study contributes valuable evidence toward improving diagnostic accuracy and therapeutic outcomes for individuals affected by ACC.

Strength

1. This study evaluated the clinical relevance of positive allergens, providing more meaningful insights compared to studies that report patch test results without clinical correlation.

2. All participants completed day 7 readings, ensuring comprehensive and reliable follow-up data with no missing results.

3. Personal product testing was incorporated, allowing for individualized assessment and enhancing diagnostic accuracy.

Limitations

Despite the comprehensive nature of this study, several limitations should be considered when interpreting the findings:

1. Sample size and cohort representation:

This study included 80 participants, which is a relatively small sample size for drawing generalizable conclusions. A larger cohort would enable more robust statistical analyses and increase the external validity of the findings. Furthermore, the study population was predominantly female, limiting the applicability of the results to male patients. Future studies should strive for a more balanced gender distribution to better represent the broader population affected by allergic contact cheilitis (ACC).

2. Cross-sectional design:

The cross-sectional nature of the study provides a snapshot of allergen sensitivities at a single point in time. This design does not permit the evaluation of temporal changes in sensitization patterns or causal relationships between specific allergens and the onset or exacerbation of ACC. Longitudinal research is warranted to assess the progression of allergic responses and the effects of cumulative allergen exposure.

3. Uncontrolled confounding factors:

The study did not account for all potential confounding variables that might influence allergen sensitization, such as lifestyle behaviors (e.g., diet, smoking), environmental exposures, or occupational factors. These elements could impact the

prevalence and severity of contact cheilitis and should be systematically addressed in future investigations to clarify the multifactorial etiology of the condition.

Recommendations

1. Larger, more diverse cohorts:

Future studies should include larger and more demographically diverse populations to enhance the generalizability of findings. A balanced gender distribution and a broader age range are particularly important to ensure that insights are applicable across various subgroups.

2. Longitudinal study designs:

To better understand the natural history and progression of ACC, longitudinal studies are recommended. Such studies can track changes in allergen sensitivities over time and help determine causal links between allergen exposure and clinical manifestations.

3. Assessment of confounding factors:

Future research should incorporate potential confounders such as environmental conditions, lifestyle habits, occupational exposures, and medication use. Controlling for these factors will allow for a more precise evaluation of the risk factors associated with ACC and allergic contact dermatitis.

4. Enhanced patch testing protocols:

As the prevalence of allergic contact dermatitis and cheilitis rises, refinement of patch testing protocols is essential. Expanding the allergen panels, repeating patch tests over time, and incorporating region-specific allergens may improve diagnostic sensitivity and relevance.

5. Education and awareness:

Increasing awareness among both patients and healthcare providers regarding ACC is critical. Educational efforts should emphasize the identification of common allergens in cosmetic and personal care products, the importance of early patch testing, and the potential harms of continued allergen exposure in daily-use items.

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