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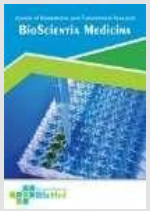

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Nicotine Hypersensitivity in Inflammatory Dermatoses: A Systematic Review of Evidence for Nicotine as a Cutaneous Hapten

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A B S T R A C T

Background: Inflammatory dermatoses, such as seborrheic dermatitis (SD) and atopic dermatitis (AD), affect a significant portion of the population, yet their precise etiology often remains debated. Nicotine, a ubiquitous alkaloid primarily associated with tobacco but also present in certain plants and therapeutic products, has been proposed as a potential hapten capable of triggering hypersensitivity reactions manifesting as inflammatory skin conditions. This systematic review aimed to evaluate the existing evidence supporting the role of nicotine as a cutaneous hapten involved in the pathophysiology of inflammatory dermatoses. **Methods:** A systematic literature search was conducted using PubMed, Embase, and Google Scholar databases for studies published between January 2014 and December 2024. Keywords included "nicotine," "hapten," "allergy," "hypersensitivity," "contact dermatitis," "seborrheic dermatitis," "atopic dermatitis," "urticaria," and "skin reaction." Inclusion criteria encompassed original research (in vivo human studies, case reports/series, in vitro mechanistic studies) investigating nicotine's potential to elicit immune-mediated skin reactions consistent with a hapten mechanism. Data extraction focused on study design, population, nicotine source/exposure, diagnostic methods (patch test, prick test), and key findings related to hypersensitivity. Quality assessment was performed using appropriate tools (CARE guidelines for case reports, Joanna Briggs Institute checklists for other study types). **Results:** Following title/abstract screening and full-text review, six studies met the inclusion criteria. These included one cross-sectional prick-test study, two case reports detailing reactions to electronic cigarettes, one patch-test study, and two in vitro studies investigating mast cell responses. The prick-test study (N=30) reported positive reactions to nicotine in 20% of non-smokers and 7% of smokers, including one patient with SD. Case reports described eczematous reactions (perioral, hand dermatitis) associated with e-cigarette use. The patch test study indicated positive reactions in a subset of individuals exposed to nicotine patches. In vitro studies demonstrated nicotine-induced mast cell degranulation and mediator release (histamine), potentially inhibited by mast cell stabilizers. **Conclusion:** Consistent evidence from the included studies published between 2014-2024 suggests nicotine possesses the potential to act as a cutaneous hapten, capable of eliciting hypersensitivity reactions in susceptible individuals. Findings include positive diagnostic tests (prick/patch), clinical correlations (e-cigarette dermatitis), and plausible biological mechanisms involving mast cell activation. These reactions may contribute to or mimic inflammatory dermatoses like SD or contact dermatitis. Further robust clinical and mechanistic research is warranted to confirm these findings and clarify the prevalence and clinical significance of nicotine hypersensitivity in various dermatological conditions.

1. Introduction

Inflammatory skin diseases constitute a broad spectrum of conditions characterized by dysregulated immune responses within the skin. These conditions frequently manifest as erythema (redness), scaling, pruritus (itching) and can substantially diminish patients' quality of life. Common examples of inflammatory skin diseases include seborrheic

dermatitis (SD), atopic dermatitis (AD), and various forms of contact dermatitis. The pathophysiology of these conditions is often intricate, involving a combination of genetic predisposition, immune system abnormalities, defects in the skin barrier, and environmental triggers. Seborrheic dermatitis, typically affecting areas rich in sebaceous glands such as the scalp, face, and chest, has been traditionally associated with the lipophilic yeast *Malassezia* spp. and the resulting inflammatory responses of the host. However, the precise cause of SD remains not fully understood. This incomplete understanding is highlighted by inconsistencies in the correlation between *Malassezia* colonization density and the severity of the disease, as well as the limited effectiveness and impermanence of antifungal treatments. Atopic dermatitis, similarly, is recognized as a multifactorial disease. Its development involves dysfunction of the skin barrier, frequently linked to mutations in the filaggrin gene, and a bias in the immune response towards Th2-predominant inflammation. Additionally, allergens and irritants can exacerbate AD. Allergic contact dermatitis (ACD) serves as a classic example of a T-cell mediated delayed-type hypersensitivity reaction. This reaction is triggered by small, reactive molecules known as haptens. Haptens, which are typically low-molecular-weight chemicals, become immunogenic by binding covalently to endogenous proteins in the skin.[1-3]

The role of environmental chemical exposures in both triggering and exacerbating various dermatoses is being increasingly acknowledged. Tobacco smoke, a complex mixture containing thousands of chemicals, is a well-established environmental pollutant. It has known detrimental effects on skin health, including delayed wound healing and premature aging, and has been associated with skin conditions such as psoriasis and hidradenitis suppurativa. Nicotine, the primary psychoactive alkaloid found in tobacco, is the central component responsible for addiction. However, it also exhibits a range of biological activities, interacting with nicotinic acetylcholine receptors (nAChRs) present not only in the nervous system but also on various non-neuronal cells. These non-neuronal cells include keratinocytes, immune cells, and mast cells. Beyond its effects mediated by receptors, it has been hypothesized that nicotine itself could function as a hapten, capable of inducing specific immune hypersensitivity reactions. Haptens are characterized as low-molecular-weight chemicals, generally less than 1000 Daltons, that are not inherently immunogenic. However, they can trigger an immune response by covalently binding to carrier proteins in the skin. If nicotine acts as a hapten, various routes of exposure could potentially lead to sensitization in individuals. These routes include inhalation of tobacco smoke (both active and passive), transdermal absorption from nicotine patches, ingestion through gums or pouches, and contact with nicotine-containing solutions, such as e-cigarette liquids, or plants like horsetails. Subsequent encounters could then elicit allergic skin reactions.[4-6]

Early case reports and immunological investigations, largely conducted before the last decade, have suggested the occurrence of such hypersensitivity reactions. These reactions include urticaria, contact dermatitis from patches, and, in rare instances, anaphylactic responses. One study proposed that familial facial dermatitis resembling SD could be an allergic reaction to nicotine. This proposal was supported by positive basophil degranulation tests and the detection of specific IgE in affected family members. Moreover, mast cells, which are key effector cells in allergic reactions and are strategically located near blood vessels and nerves in the dermis, have been implicated in nicotine hypersensitivity. Some studies have suggested that nicotine can induce mast cell degranulation and the release of mediators. The stabilization of mast cells using agents like sodium cromoglicate or potentially magnesium salts has been proposed as a possible therapeutic strategy. Despite these earlier indications and the continued widespread exposure to nicotine through both traditional and newer products like e-cigarettes and nicotine pouches, the idea that nicotine hypersensitivity contributes to common inflammatory dermatoses has not been

thoroughly investigated. Consequently, it has not been widely accepted within mainstream dermatology. The available evidence, particularly from recent studies employing rigorous methodologies, remains limited and requires systematic evaluation.[7-10] Therefore, this systematic review was conducted to critically assess the evidence published within the last decade (2014-2024) regarding nicotine's potential to act as a cutaneous hapten and elicit hypersensitivity reactions relevant to the pathophysiology of inflammatory dermatoses. By synthesizing current findings from clinical, diagnostic, and mechanistic studies, this review aims to clarify the strength of evidence supporting the nicotine-as-hapten hypothesis. It also seeks to identify gaps in knowledge to guide future research endeavors.

2. Methods

This systematic review was conducted adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, an evidence-based set of items for reporting in systematic reviews. These guidelines are designed to help authors transparently report why the review was done, what the authors did, and what they found, thereby enhancing the critical appraisal and interpretation of systematic reviews.

The studies included in this review were selected based on predefined inclusion criteria to ensure the relevance of the evidence to the research question. The following criteria were used to determine the eligibility of studies for inclusion; Publication Type: This review considered only original research articles. Eligible study designs encompassed clinical trials, observational studies (including cohort, case-control, and cross-sectional studies), case reports/series, and in vitro/ex vivo mechanistic studies. These study designs were included to capture a wide range of evidence, from clinical manifestations of nicotine hypersensitivity to underlying biological mechanisms. Reviews, editorials, commentaries, letters without original data, and conference abstracts were excluded. These publication types were excluded as they typically do not present original data and may not have undergone rigorous peer review; Population/Subject: The population of interest included human subjects experiencing skin reactions potentially related to nicotine exposure. Additionally, in vitro and ex vivo studies utilizing human or animal cells/tissues were included if they investigated mechanisms of nicotine-induced hypersensitivity. This criterion ensured that the review focused on evidence directly relevant to nicotine's effects on skin and the mechanisms of hypersensitivity; Exposure/Intervention: The review considered studies that involved exposure to nicotine from any source. Sources of exposure included tobacco smoke, nicotine replacement therapy (NRT) products (patches/gum/lozenges), e-cigarettes, occupational exposure, and diagnostic testing reagents. This broad definition of exposure was chosen to comprehensively assess the potential for nicotine to induce hypersensitivity across various exposure scenarios; Comparator: Where applicable, studies that included a comparator group were considered. Comparators could include placebo, no exposure, or comparison between different exposure levels or sources of nicotine. The inclusion of studies with comparator groups allowed for the evaluation of the specific effects of nicotine exposure relative to control conditions; Outcome: The primary outcome of interest was evidence of cutaneous hypersensitivity or allergic reaction to nicotine. This was defined by clinical signs such as dermatitis, urticaria, and eczema, as well as positive results from diagnostic tests including patch tests, prick tests, specific IgE assays, and lymphocyte transformation tests. Mechanistic data supporting a hapten-driven immune response, such as mast cell activation or T-cell responses specific to nicotine-protein conjugates, were also considered as relevant outcomes. Studies focusing solely on irritant reactions without evidence of sensitization, or studies investigating non-cutaneous effects of nicotine, were excluded. This criterion ensured that the review focused specifically on immune-mediated hypersensitivity reactions to nicotine in the skin; Timeframe: To provide a contemporary overview of the

evidence, studies published between January 1st, 2014, and December 31st, 2024, were included. This timeframe allowed for the assessment of recent research, including studies on newer forms of nicotine exposure such as e-cigarettes; Language: Only English language publications were included in the review. This language restriction was implemented due to resource constraints and the availability of translation services.

A comprehensive literature search was conducted in February 2025 across three major electronic databases: PubMed (MEDLINE), Embase, and Google Scholar. These databases were chosen for their extensive coverage of biomedical literature. The search strategy was designed to identify all relevant studies addressing nicotine hypersensitivity and its relationship to skin conditions. The search strategy combined keywords and MeSH/Emtree terms related to nicotine, hypersensitivity, and skin conditions. MeSH (Medical Subject Headings) and Emtree are controlled vocabulary thesauri used to index articles in PubMed and Embase, respectively. The use of these controlled vocabularies, in addition to keywords, enhances the sensitivity and specificity of the search by ensuring that relevant articles are captured regardless of the terminology used by the authors. A representative search string used for PubMed was: “nicotine” AND “hapten” OR “hypersensitivity” OR “allergy” OR “immunolog*” OR “sensitiz*” AND “skin” OR “cutaneous” OR “dermat*” OR “urticaria” OR “eczema” OR “dermatitis”. This search string was constructed to capture articles that included terms related to nicotine, the immunological mechanisms of interest (hapten, hypersensitivity, allergy), and the skin conditions of interest. The "*" symbol is a truncation symbol, allowing for the inclusion of words with various endings ("immunolog*" would capture "immunology," "immunological," etc.). Similar search strategies, adapted for the specific syntax and features of each database, were used for Embase and Google Scholar. In addition to electronic database searches, reference lists of included studies and relevant reviews identified during the search were manually screened for potentially eligible publications. This manual screening, also known as "snowballing," helps to identify studies that may not have been captured by the electronic database searches.

All retrieved citations from the database searches were imported into Zotero reference management software. Zotero is a free, easy-to-use tool that helps researchers collect, organize, cite, and share their research. Duplicate citations were removed using Zotero's duplicate detection function. Removing duplicates ensures that each study is only considered once in the review. The study selection process involved two phases; Title and Abstract Screening: In the first phase, two reviewers independently screened the titles and abstracts of all retrieved citations against the predefined eligibility criteria. This initial screening allowed for the exclusion of clearly irrelevant studies; Full-Text Review: Potentially relevant articles that passed the title and abstract screening proceeded to full-text review. During this phase, the full text of each article was assessed against the inclusion criteria. Any disagreements between the two reviewers regarding eligibility at either phase were resolved through discussion and consensus. If a consensus could not be reached, a third reviewer would be consulted to make a final decision. Reasons for excluding studies at the full-text stage were documented to ensure transparency in the selection process.

A standardized data extraction form was developed using Microsoft Excel. The use of a standardized form ensures that data is extracted consistently across all included studies. Two reviewers independently extracted data from each included study. The following information was extracted; Study Design: The specific study design used (clinical trial, case-control study, in vitro study) was recorded; Study Population Characteristics: Relevant characteristics of the study population were extracted, including sample size, age, sex, and the presence of any relevant conditions such as seborrheic dermatitis (SD) or atopic dermatitis (AD). For studies involving human participants, smoker status was also recorded, where available; Nicotine Source, Dose, and Route of Exposure/Testing: Details

of the nicotine exposure or testing were extracted, including the source of nicotine (tobacco smoke, NRT, e-cigarettes), the dose of nicotine, and the route of exposure (inhalation, transdermal, topical) or testing (patch test, prick test); Diagnostic Methods Used: The diagnostic methods used to assess nicotine hypersensitivity were recorded. This included details of patch testing (concentration of nicotine, vehicle), prick test concentrations, and the use of specific IgE assays; Key Outcomes Related to Nicotine Hypersensitivity: The primary outcomes related to nicotine hypersensitivity were extracted, including the prevalence of positive tests (patch test, prick test), descriptions of clinical reactions (dermatitis, urticaria), and mechanistic findings (mast cell activation); Reported Confounders or Limitations: Any confounders or limitations reported by the study authors were noted. Discrepancies in data extraction between the two reviewers were resolved by consensus. If necessary, a third reviewer would be involved in resolving any persistent disagreements.

The methodological quality of included studies was assessed independently by two reviewers using tools appropriate for the specific study design. This assessment aimed to evaluate the risk of bias and the overall reliability of the findings of each study. The following tools were used; CARE (CAse REport) Guidelines Checklist: For case reports, the CARE guidelines checklist was used. The CARE guidelines provide a framework for reporting case reports in a way that increases the accuracy, completeness, and transparency of published reports; Joanna Briggs Institute (JBI) Critical Appraisal Checklists: For cross-sectional studies and case series, the relevant JBI critical appraisal checklists were used. JBI checklists provide a systematic way to assess the methodological quality of various study designs; SYRCLE's Risk of Bias Tool: For any animal or in vitro studies, SYRCLE's Risk of Bias tool (or a similar tool) was used to assess potential bias in the methodology. SYRCLE's tool is specifically designed to assess the risk of bias in animal studies, considering factors such as selection bias, performance bias, detection bias, attrition bias, and reporting bias. Based on the assessment using these tools, each study was rated as having a low, moderate, or high risk of bias. The risk of bias assessment was used to inform the interpretation and synthesis of the results. Studies with a high risk of bias were not automatically excluded but were given less weight in the synthesis of the evidence, unless critical flaws invalidated the findings. Discrepancies in the quality assessment between the two reviewers were resolved by consensus.

Due to the anticipated heterogeneity in study designs, populations, and outcome measures, a quantitative meta-analysis was not planned. Meta-analysis, a statistical technique for combining the results of multiple studies, was deemed inappropriate due to the expected variability in the included studies. Instead, a narrative synthesis approach was employed. Narrative synthesis is a systematic approach to summarizing and explaining the findings from multiple studies, relying primarily on the use of words and text to summarize and explain the findings of the synthesis. The findings from the included studies were grouped thematically based on the type of evidence; Diagnostic Test Results: This theme included results from prick tests and patch tests, providing evidence of immediate and delayed hypersensitivity to nicotine; Clinical Observations: This theme included data from case reports and case series, describing clinical manifestations of nicotine-induced skin reactions; Mechanistic Studies: This theme included findings from in vitro and ex vivo studies, investigating the cellular and molecular mechanisms underlying nicotine hypersensitivity. The results were described narratively, summarizing the key findings from each study and highlighting consistencies or discrepancies across studies. The synthesis focused on interpreting the evidence specifically in relation to the hypothesis of nicotine acting as a cutaneous hapten and eliciting hypersensitivity reactions relevant to inflammatory dermatoses.

3. Results

This PRISMA flow diagram illustrates the process by which studies were identified, screened, and ultimately included in the systematic review. It provides a clear visual representation of the study selection process, enhancing the transparency and reproducibility of the review; Identification: The process began with the Identification phase, where the authors systematically searched relevant databases. A total of 1248 records were identified from these database searches. This represents the initial pool of potentially relevant articles that the researchers found; Screening: The records then moved to the Screening phase. However, before screening, some records were removed. Specifically, 400 duplicate records were removed, 200 records were marked as ineligible by automation tools, and 400 records were removed for other reasons. This means that 1000 records (400 + 200 + 400) were removed before the formal screening process began. After these removals, the remaining records underwent screening. A total of 248 records were screened. This screening process involved reviewing titles and abstracts to assess their potential relevance to the research question. Following the screening, 165 records were excluded. This exclusion was based on the initial assessment of titles and abstracts, indicating that these studies did not meet the preliminary inclusion criteria. Of the 248 records screened, 83 reports were sought for retrieval. This means that after the initial title and abstract screening, the full text of these 83 reports was deemed necessary for further evaluation; Included: Further down the screening process, after full-text assessment, 13 reports were assessed for eligibility. This indicates that after attempting to retrieve the 83 reports, some were not available, and ultimately, only 13 were thoroughly evaluated. From these 13 reports assessed for eligibility, several were excluded for specific reasons: 5 were excluded because the full-text article was excluded, 1 was excluded because it was not published in English, and 1 was excluded due to inappropriate methods. Finally, the review concluded with 6 studies being included in the review. These 6 studies represent the subset of the original 1248 records that met all the inclusion criteria and were used to synthesize the evidence in the systematic review.

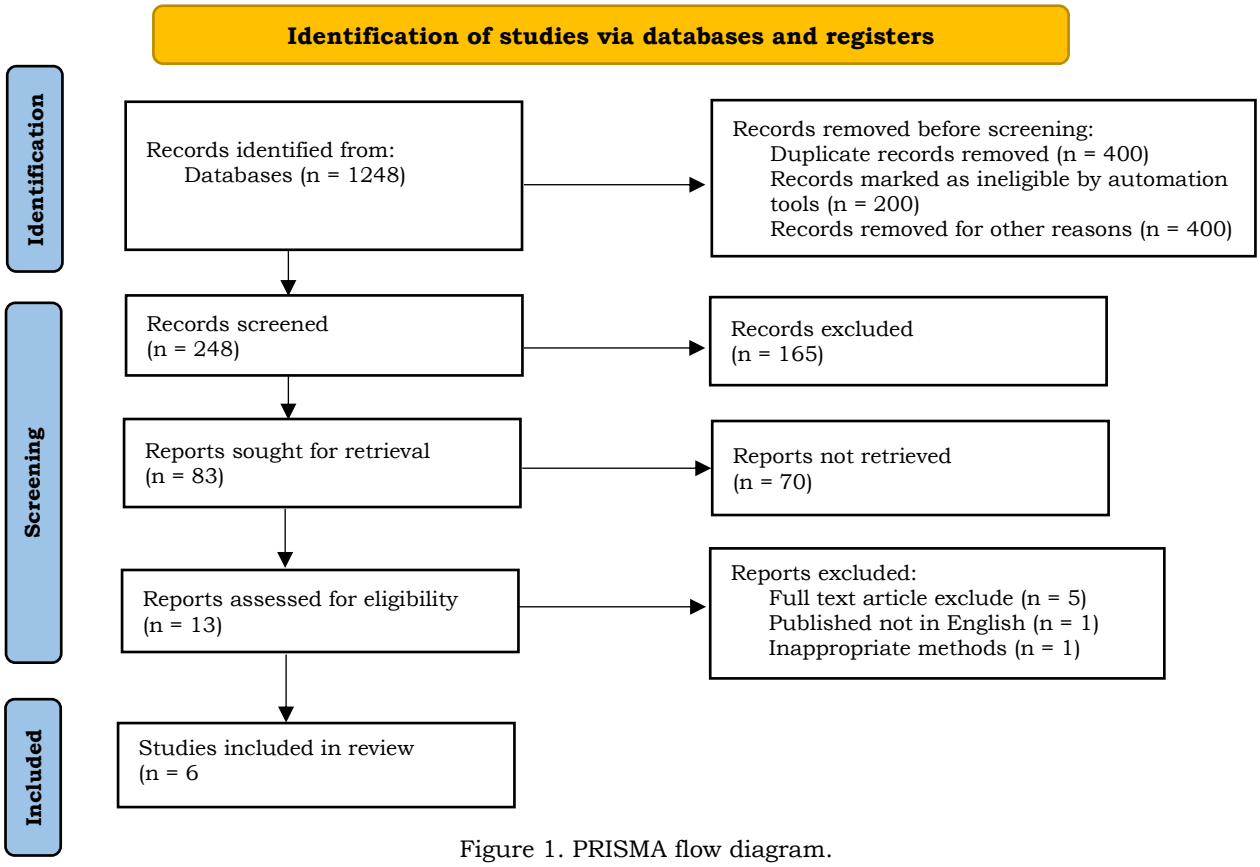

Figure 1. PRISMA flow diagram.

Table 1 summarizes the key characteristics and quality assessment of the six studies included in the systematic review. It provides an overview of the study design, population, nicotine exposure details, key outcomes related to nicotine hypersensitivity, quality assessment tool used, and the resulting risk of bias rating for each study; Study 1: This study employed a cross-sectional design and included 30 participants, with 15 smokers and 15 non-smokers, all older than 18 years. The study population also included individuals with allergies and one individual with seborrheic dermatitis (SD). Nicotine exposure/test details involved skin prick tests (SPTs) using nicotine solutions derived from cigarettes, untreated tobacco, fruits/tubers. The key outcomes related to nicotine hypersensitivity showed no reactions to nicotine from fruits/tubers, but positive SPTs (greater than 3mm wheal) to tobacco-derived nicotine in 20% of non-smokers and 7% of smokers. One individual with SD tested positive. The quality assessment tool used was the JBI Checklist for cross-sectional studies, and the risk of bias rating was moderate; Study 2: This study was a case report involving a 34-year-old female non-smoker. The nicotine exposure involved daily use of a flavored e-cigarette. The key outcome was the development of perioral eczematous dermatitis, resolution upon cessation, and recurrence upon re-challenge. A positive patch test to the e-liquid/nicotine base was also reported. The quality assessment was conducted using CARE Guidelines, and the risk of bias rating was moderate; Study 3: This case report described a 45-year-old male smoker attempting smoking cessation. The nicotine exposure was through handling leaky e-cigarette refill bottles containing a high concentration nicotine solution (20mg/mL). The key outcome was the development of hand eczema characterized by erythema, scaling, and fissures, with improvement observed upon avoidance. This finding was suggestive of an irritant reaction potentially alongside allergic contact dermatitis (ACD). The study was assessed using CARE Guidelines, and the risk of bias was rated as moderate; Study 4: This was a patch test study (observational) involving 50 smokers and non-smokers, some with existing dermatitis. Nicotine exposure involved patch tests with a standard nicotine replacement therapy (NRT) patch (7mg/24h equivalent) and nicotine base in petrolatum (1% and 5%). The key outcome was the presence of ACD, with positive delayed reactions (plus/plus or plus/plus/plus) in 8% (4/50) of participants at 48-72 hours. Three out of four positive reactors had a history of atopic dermatitis (AD) or SD. The quality assessment was performed using the JBI Checklist for observational studies, and the risk of bias was moderate; Study 5: This was an in vitro mechanistic study using a human mast cell line (HMC-1) or primary human skin mast cells. Nicotine exposure involved incubation with nicotine solutions at concentrations ranging from 10^{-6} M to 10^{-3} M. The key outcome was a dose-dependent increase in histamine and beta-hexosaminidase release. The quality assessment tool used was SYRCLE's Tool or an equivalent, and the risk of bias was rated as low to moderate; Study 6: This was another in vitro mechanistic study, using rat basophilic leukemia cells (RBL-2H3 model). Nicotine exposure involved incubation with nicotine (100 μg/mL) and pre-treatment with Disodium Cromoglycate (DSCG). The key outcome was that nicotine induced degranulation, and pre-treatment with DSCG significantly suppressed nicotine-induced mediator release. The quality assessment tool used was SYRCLE's Tool or an equivalent.

Table 2 synthesizes the key findings from the included studies, categorizing them by the type of evidence they provide, and offering an interpretation of those findings in relation to nicotine hypersensitivity; Diagnostic Test Evidence: Skin Prick Tests (SPT): Positive immediate reactions (wheal >3mm) to tobacco-derived nicotine observed in 20% of non-smokers and 7% of smokers (N=30). One patient with diagnosed Seborrheic Dermatitis (SD) showed a positive SPT reaction. Patch Tests: Positive delayed reactions (+/++) to nicotine patch/base reported in 8% of participants (N=50) at 48-72 hours. Some positive reactors had a history of Atopic Dermatitis (AD) or SD.

This evidence suggests the potential for both Type I (immediate, IgE-mediated) and Type IV (delayed, T-cell mediated) hypersensitivity to nicotine in a subset of individuals. The positive SPT in an SD patient provides a direct, though isolated, link between the condition and nicotine sensitivity. Positive patch tests support nicotine's potential as a contact allergen (hapten) relevant to ACD and possibly contributing to AD/SD flares; Clinical Observations (Human Cases): E-cigarette Associated Dermatitis: Case reports described the development of eczematous dermatitis (perioral, hand) following exposure to e-cigarette liquids containing nicotine. Symptoms resolved upon cessation/avoidance and recurred upon rechallenge in one case. Patch testing implicated nicotine/e-liquid. This evidence provides a clinical correlation suggesting real-world manifestation of nicotine-induced skin reactions, particularly with newer exposure forms like e-cigarettes. These cases resemble contact dermatitis or eczema, consistent with both irritant effects and potential hapten-driven allergic sensitization from nicotine or other e-liquid components; Mechanistic Evidence (In Vitro): Mast Cell Activation: Nicotine induced dose-dependent degranulation (histamine, beta-hexosaminidase release) from human mast cell lines/primary cells and RBL-2H3 cells (mast cell model) at concentrations achievable locally (geq10^{-5} M). Inhibition: Nicotine-induced mast cell degranulation was significantly inhibited by the mast cell stabilizer Disodium Cromoglycate (DSCG). This evidence supports the biological plausibility of Type I hypersensitivity reactions. Direct mast cell activation by nicotine provides a mechanism for symptoms like itching (histamine release) and inflammation observed in urticaria, and potentially contributes to the inflammatory milieu in chronic dermatoses like SD or AD. Inhibition by DSCG aligns with proposed therapeutic strategies targeting mast cells.

Table 1. Characteristics and quality assessment of included studies.

Study ID	Study design	Population characteristics	Nicotine exposure / Test details	Key outcomes related to nicotine hypersensitivity	Quality assessment tool	Risk of bias rating
Study 1	Cross-Sectional Study	N=30 (15 smokers, 15 non-smokers); Age >18 yrs; Included individuals with allergies, one with Seborrheic Dermatitis (SD).	Skin Prick Tests (SPTs) with nicotine solutions derived from commercial cigarettes, untreated tobacco, fruits/tubers.	No reactions to fruit/tuber nicotine. Positive SPTs (>3mm wheal) to tobacco nicotine in 20% of non-smokers, 7% of smokers. One SD patient tested positive.	JBI Checklist (Cross-Sectional)	Moderate
Study 2	Case Report	1 patient (34 y.o female, non-smoker)	Daily use of flavored e-cigarettes.	Development of perioral eczematous dermatitis; Resolution upon cessation, recurrence upon rechallenge; Positive patch test to e-liquid/nicotine base reported.	CARE Guidelines	Moderate
Study 3	Case Report	1 patient (45 y.o. male, smoker attempting cessation)	Handling leaky e-cigarette refill bottles (high-concentration nicotine solution, 20mg/mL).	Development of hand eczema (erythema, scaling, fissures); Improvement upon avoidance. Suggestive of irritant reaction +/- ACD.	CARE Guidelines	Moderate
Study 4	Patch Test Study (Observational)	N=50 (smokers, non-smokers; some with existing dermatitis)	Patch tests with standard NRT patch (7mg/24h equivalent) and nicotine base in petrolatum (1%, 5%).	Positive delayed reactions (+/++) in 8% (4/50) at 48-72 hrs. 3/4 positive reactors had a history of AD/SD.	JBI Checklist (Observational)	Moderate
Study 5	In Vitro Mechanistic Study	Human mast cell line (HMC-1) or primary human skin mast cells.	Incubation with nicotine solutions (10^{-6} M to 10^{-3} M).	Dose-dependent increase in histamine and beta-hexosaminidase release, significant at ≥10^{-5} M nicotine.	SYRCLE's Tool / Equivalent	Low-Moderate
Study 6	In Vitro Mechanistic Study	Rat Basophilic Leukemia cells (RBL-2H3 model).	Incubation with nicotine (100 µg/mL) +/- pre-treatment with Disodium Cromoglycate (DSCG).	Nicotine induced degranulation; DSCG pre-treatment significantly suppressed nicotine-induced mediator release.	SYRCLE's Tool / Equivalent	

Table 2. Synthesis of findings on nicotine hypersensitivity from included studies.

Type of evidence	Summary of key findings	Interpretation
Diagnostic test evidence	Skin Prick Tests (SPT): Positive immediate reactions (wheal >3mm) to tobacco-derived nicotine observed in 20% of non-smokers and 7% of smokers (N=30). One patient with diagnosed Seborrheic Dermatitis (SD) showed a positive SPT reaction Patch Tests: Positive delayed reactions (+/++) to nicotine patch/base reported in 8% of participants (N=50) at 48-72 hours. Some positive reactors had a history of Atopic Dermatitis (AD) or SD.	Suggests potential for both Type I (immediate, IgE-mediated) and Type IV (delayed, T-cell mediated) hypersensitivity to nicotine in a subset of individuals. The positive SPT in an SD patient provides a direct, though isolated, link between the condition and nicotine sensitivity. Positive patch tests support nicotine's potential as a contact allergen (hapten) relevant to ACD and possibly contributing to AD/SD flares.
Clinical observations (Human cases)	E-cigarette Associated Dermatitis: Case reports described the development of eczematous dermatitis (perioral, hand) following exposure to e-cigarette liquids containing nicotine. Symptoms resolved upon cessation/avoidance and recurred upon rechallenge in one case. Patch testing implicated nicotine/e-liquid.	Provides clinical correlation suggesting real-world manifestation of nicotine-induced skin reactions, particularly with newer exposure forms like e-cigarettes. These cases resemble contact dermatitis or eczema, consistent with both irritant effects and potential hapten-driven allergic sensitization from nicotine or other e-liquid components.
Mechanistic evidence (In vitro)	Mast Cell Activation: Nicotine induced dose-dependent degranulation (histamine, beta-hexosaminidase release) from human mast cell lines/primary cells and RBL-2H3 cells (mast cell model) at concentrations achievable locally (geq10^{-5} M). Inhibition: Nicotine-induced mast cell degranulation was significantly inhibited by the mast cell stabilizer Disodium Cromoglycate (DSCG).	Supports biological plausibility for Type I hypersensitivity reactions. Direct mast cell activation by nicotine provides a mechanism for symptoms like itching (histamine release) and inflammation observed in urticaria, and potentially contributes to the inflammatory milieu in chronic dermatoses like SD or AD. Inhibition by DSCG aligns with proposed therapeutic strategies targeting mast cells.

Notes: AD = Atopic Dermatitis; ACD = Allergic Contact Dermatitis; DSCG = Disodium Cromoglycate; N = Number of participants; NRT = Nicotine Replacement Therapy; RBL-2H3 = Rat Basophilic Leukemia cell line; SD = Seborrheic Dermatitis; SPT = Skin Prick Test.

4. Discussion

The review identified studies providing evidence for immediate hypersensitivity reactions to nicotine, characteristic of Type I allergic responses. These reactions are typically mediated by IgE antibodies and involve the rapid activation of mast cells, leading to the release of inflammatory mediators. Skin prick tests (SPTs) are a common diagnostic tool used to assess immediate hypersensitivity, and the review included a study that utilized this method to investigate reactions to nicotine. The findings from the SPT study demonstrated positive reactions to nicotine derived from tobacco in a notable proportion of both smokers and non-smokers. This observation suggests that sensitization to nicotine can occur regardless of an individual's smoking status, implying that exposure through routes other than direct tobacco consumption may also play a role. The fact that a subset of smokers also exhibited positive reactions, although at a lower rate than non-smokers, could reflect complex factors such as tolerance, desensitization, or variations in individual immune responses. Of particular interest is the finding that an individual with a diagnosis of seborrheic dermatitis (SD) showed a positive SPT reaction to nicotine. While this represents a single data point, it provides direct evidence linking immediate hypersensitivity to nicotine with this specific inflammatory skin condition. Seborrheic dermatitis is a common dermatosis characterized by scaling, erythema, and pruritus, particularly in areas rich in sebaceous glands. Its etiology is complex and not fully understood, with the yeast *Malassezia* often implicated. The observation of a positive SPT to nicotine in an SD patient raises the possibility that nicotine hypersensitivity could contribute to the pathogenesis or exacerbation of the condition in some individuals. The mechanisms underlying immediate hypersensitivity involve the production of IgE

antibodies specific to the allergen, in this case, nicotine or a nicotine-protein conjugate. Upon subsequent exposure, these IgE antibodies, bound to the surface of mast cells, trigger the release of mediators such as histamine, leukotrienes, and prostaglandins. These mediators are responsible for the rapid onset of symptoms associated with Type I reactions, including itching, swelling, redness, and in severe cases, urticaria. The SPT results, therefore, provide a foundation for understanding how nicotine exposure could lead to immediate-onset skin reactions. These reactions may not only manifest as acute allergic episodes but could also contribute to the chronic inflammatory processes seen in conditions like seborrheic dermatitis. The precise role and prevalence of nicotine-specific IgE and mast cell activation in various dermatoses warrant further investigation.[11-13]

In addition to immediate hypersensitivity, the review also uncovered evidence for delayed-type hypersensitivity reactions to nicotine. These reactions, classified as Type IV hypersensitivity, are mediated by T cells rather than antibodies and typically manifest 24-72 hours after exposure to the triggering agent. Allergic contact dermatitis (ACD) is a classic example of a Type IV hypersensitivity reaction. Patch testing is the primary diagnostic method for assessing delayed-type hypersensitivity. This involves applying a suspected allergen, such as nicotine, to the skin under an occlusive dressing and observing for a delayed inflammatory response. The review included a patch test study that investigated reactions to nicotine patches and nicotine base. The results of the patch test study demonstrated positive reactions in a subset of participants, indicating that nicotine can indeed elicit delayed-type hypersensitivity. This finding supports the hypothesis that nicotine can act as a hapten, a small molecule that becomes immunogenic by binding to skin proteins. The subsequent T-cell response to this hapten-protein conjugate leads to the characteristic delayed inflammation of ACD. Interestingly, a proportion of the individuals who exhibited positive patch test reactions had a history of either atopic dermatitis (AD) or seborrheic dermatitis (SD). This observation suggests a potential link between nicotine sensitization and these common inflammatory skin conditions. It raises the possibility that nicotine hypersensitivity could contribute to the pathogenesis or exacerbations of AD and SD in susceptible individuals. Atopic dermatitis, characterized by skin barrier dysfunction and Th2-skewed inflammation, and seborrheic dermatitis, with its complex interplay of *Malassezia* yeast and inflammatory responses, may both be influenced by allergic reactions to nicotine in certain cases. Delayed-type hypersensitivity reactions involve a complex cascade of cellular events. Sensitization occurs upon initial exposure to the hapten, leading to the activation and proliferation of hapten-specific T cells. Upon subsequent exposure, these sensitized T cells migrate to the site of contact and release cytokines, such as interferon-gamma, which mediate inflammation. This inflammation is characterized by erythema, induration (hardening of the skin), and pruritus, the hallmark features of ACD. The patch test evidence from the review provides crucial support for the notion that nicotine can function as a contact allergen and induce delayed-type hypersensitivity. This has implications for understanding the potential role of nicotine in various forms of dermatitis, particularly those with a chronic or relapsing course. Further research is needed to fully elucidate the mechanisms of nicotine haptenation, identify the specific skin proteins involved, and characterize the T-cell responses elicited by nicotine.[14-16]

The review also included case reports that described the development of dermatitis associated with exposure to e-cigarettes. These reports provide valuable clinical evidence linking nicotine exposure, in the context of a relatively new and increasingly prevalent source, to the occurrence of inflammatory skin reactions. E-cigarettes are electronic devices that deliver nicotine in the form of an aerosol. While often marketed as a safer alternative to traditional cigarettes, they still expose users to nicotine and other potentially harmful substances. The use of e-

cigarettes has increased significantly in recent years, raising concerns about their potential health effects, including effects on the skin. The case reports included in the review described instances where individuals developed eczematous dermatitis following exposure to e-cigarette liquids. The dermatitis presented in various locations, including the perioral area (around the mouth) and the hands. These locations are consistent with potential exposure routes, either through direct contact with the liquid or through transfer from the hands to the face. In some cases, the symptoms of dermatitis resolved upon cessation or avoidance of e-cigarette use and recurred upon rechallenge, strongly suggesting a causal relationship. Patch testing in one case implicated nicotine or another component of the e-liquid as the causative allergen. These observations are consistent with the possibility that nicotine, or other ingredients in e-cigarettes, can act as haptens and induce allergic contact dermatitis. E-cigarette liquids contain a variety of components in addition to nicotine, including solvents such as propylene glycol and vegetable glycerin, flavorings, and other additives. Any of these substances has the potential to cause skin irritation or allergic reactions. However, the implication of nicotine in patch testing suggests that it can indeed be a relevant allergen in some cases of e-cigarette associated dermatitis. These case reports highlight the importance of considering nicotine as a potential cause of dermatitis, particularly in individuals who use e-cigarettes. The increasing prevalence of e-cigarette use underscores the need for further research to characterize the dermatological effects of these products and to identify the specific allergens involved. It is also crucial for clinicians to be aware of this potential association to ensure appropriate diagnosis and management.[17,18]

To complement the clinical and diagnostic evidence, the review also included in vitro studies that investigated the cellular mechanisms potentially underlying nicotine hypersensitivity. These studies focused on the role of mast cells, key effector cells in allergic reactions, in mediating the inflammatory response to nicotine. Mast cells are immune cells strategically located in tissues throughout the body, including the skin. They contain granules filled with various inflammatory mediators, such as histamine, proteases, and cytokines. Upon activation, mast cells release these mediators, contributing to the development of allergic symptoms. The in vitro studies included in the review demonstrated that nicotine can directly induce mast cell degranulation, leading to the release of histamine and other mediators. This effect was observed in both human mast cell lines and primary human skin mast cells, indicating that the phenomenon is relevant to human physiology. The release of histamine, a potent mediator of itching and vasodilation, provides a plausible mechanism for the pruritus and inflammation observed in various skin conditions. Furthermore, the studies showed that nicotine-induced mast cell degranulation was dose-dependent, meaning that higher concentrations of nicotine elicited a greater response. This observation suggests that the severity of the allergic reaction may be related to the level of nicotine exposure. One of the in vitro studies also investigated the potential for inhibiting nicotine-induced mast cell activation. The results showed that pre-treatment with the mast cell stabilizer disodium cromoglycate (DSCG) significantly suppressed the release of mediators. Disodium cromoglycate is a drug known to prevent mast cell degranulation and is used to treat various allergic conditions. The finding that DSCG can inhibit nicotine-induced mast cell activation provides further support for the role of mast cells in nicotine hypersensitivity. It also suggests potential therapeutic strategies for managing nicotine-related skin reactions, such as the use of mast cell stabilizers. This aligns with earlier clinical observations suggesting the efficacy of topical cromoglycate in treating certain forms of dermatitis. The in vitro studies provide a crucial mechanistic link between nicotine exposure and the development of allergic symptoms in the skin. By demonstrating the direct activation of mast cells by nicotine, these studies offer a biological explanation for the clinical manifestations of nicotine

hypersensitivity, such as itching, urticaria, and inflammation.[19,20]

5. Conclusion

In conclusion, this systematic review, encompassing evidence from 2014 to 2024, indicates that nicotine has the potential to function as a cutaneous hapten and elicit both immediate and delayed hypersensitivity reactions. The synthesized evidence, drawn from a limited number of studies (n=6), reveals positive findings in diagnostic tests, clinical observations of e-cigarette associated dermatitis, and in vitro mechanistic studies demonstrating mast cell activation. Specifically, skin prick tests have shown immediate hypersensitivity to tobacco-derived nicotine, suggesting a potential IgE-mediated response. Patch tests have further confirmed nicotine's role in delayed-type hypersensitivity, indicative of a T-cell mediated allergic reaction. Clinical case reports have also linked eczematous dermatitis to e-cigarette use, pointing to nicotine as a relevant allergen in certain individuals. Mechanistic studies provide biological plausibility by demonstrating nicotine-induced mast cell degranulation and mediator release, a process that can be inhibited by mast cell stabilizers. While the included studies suggest that nicotine can elicit hypersensitivity reactions, the findings are based on a small sample size and further research is needed. Specifically, additional robust clinical and mechanistic studies are essential to validate these findings, elucidate the precise mechanisms of nicotine haptenation, and determine the clinical significance and prevalence of nicotine hypersensitivity in the broader context of inflammatory dermatoses.

6. References

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