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The Allergy Crossroads of Subtropical Regions: Mites, Crustaceans, and the Rise of Edible Insects

Ruperto González-Pérez [1,2,*], Paloma Poza-Guedes [1,2], Manuel Alberto Figueiras-Rincón [1], Mónica Colque-Bayona [3] and Inmaculada Sánchez-Machín [1,4]

[1] Allergy Department, Hospital Universitario de Canarias, Tenerife, Spain; pozagdes@hotmail.com (P.P.-G.); manuelfigueiras@gmail.com (M.A.F.-R.); zerupean67@gmail.com (I.S.-M.)
[2] Severe Asthma Unit, Hospital Universitario de Canarias, Tenerife, Spain
[3] Allergy Department, Hospital Universitario La Paz, Madrid, Spain; monica.colque.bayona@gmail.com
[4] Allergen Immunotherapy Unit, Hospital Universitario de Canarias, Tenerife, Spain
* Correspondence: glezruperto@gmail.com (R.G.-P.); Tel.: +0034-922-677237

Abstract: Background: Edible insects (EI) are increasingly recognized as a sustainable protein source, yet concerns persist regarding allergic reactions, even in individuals without prior known consumption. This study examines the immune response profile in patients from a subtropical area to improve understanding of mite-related cross-reactivity and emerging food sensitizations. **Methods:** To assess sensitization to edible insects, we analyzed 634 patients from a tertiary care allergy institution with high perennial exposure to house dust mites and storage mites. Sensitization patterns were assessed using the ALEX²® MacroArray platform, a multiplex IgE diagnostic tool covering 282 allergens, including *Locusta migratoria* (Lm), *Acheta domesticus* (Ad), and *T. molitor* (Tm). Patients with IgE levels ≥ 0.3 kUA/L were evaluated for cross-reactivity to both mite allergens and pan-allergens. **Results**: Of the 634 patients, 138 (21.76%) exhibited IgE sensitization to at least one EI extract. Tropomyosin was the most prevalent pan-allergen (63.76%), followed by troponin-C (28.98%) and arginine-kinase (26.81%). Notably, 95.66% of EI-sensitized individuals also reacted to mite allergens. However, 23.18% lacked reactivity to common pan-allergens, suggesting alternative sensitization mechanisms. **Conclusions**: This investigation highlights regional variations in EI sensitization, where high mite exposure in subtropical climates appears to influence IgE responses to insect proteins. The findings suggest that EI sensitization is not merely incidental but represents a distinct immunological phenomenon shaped by environmental factors and allergen cross-reactivity. While the absence of food challenge data limits clinical interpretation, recognizing EI sensitization as a potential allergy risk is crucial for food safety and public health.

Keywords: novel foods; food safety; edible insects; mites; panallergens; component-resolved diagnostics; cross-reactivity

1. Introduction

On 20 January 2025, the European Commission approved UV-treated powder derived from *Tenebrio molitor* (Tm) larvae as a food ingredient for the general population under regulated conditions [1]. This decision aligns with the growing interest in edible insects (EI) as a sustainable protein source, yet it also raises concerns regarding allergenicity. The European Food Safety Authority (EFSA) has highlighted potential risks, particularly for individuals with pre-existing allergies to crustaceans, dust mites, mollusks, or components found in insect feed, mandating specific labeling requirements to mitigate these concerns and ensure consumer safety [2].

The allergenic potential of edible insects (EI) is of particular interest due to their evolutionary proximity to crustaceans and Acari, both of which contain well-characterized allergens. Research has identified proteins such as tropomyosin (TM), α-amylase, and arginine kinase (AK) as major pan-allergens capable of eliciting immune responses. These proteins exhibit IgE-binding cross-reactivity with homologous allergens found in arthropods (e.g., mites, crustaceans), mollusks, and even certain

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nematodes [3,4]. As a result, individuals with shellfish allergies may be at risk of severe allergic reactions, including anaphylaxis, when consuming edible insects. While the link between EI consumption and crustacean allergies is well established, the impact of insect-derived allergens on individuals with mite allergies remains less clear, prompting further investigation [5,6].

The concept of mite-EI syndrome is gaining attention in allergology as an increasing number of individuals sensitized to house dust mites (HDM) and storage mites report allergic reactions to insect-based foods [7,8]. Given the strong cross-reactivity between mites, crustaceans, and insects, ingestion of edible insect products could trigger symptoms ranging from mild oral allergy syndrome to life-threatening anaphylaxis [9,10]. Documented cases indicate that individuals with known HDM or crustacean allergies may later develop sensitization to mealworms, grasshoppers, or other edible insects, yet it remains uncertain whether mite sensitization alone is sufficient to induce a true food allergy [11,12]. The clinical significance of this cross-reactivity and its potential to contribute to allergic disease burden require further exploration [13].

Beyond individual sensitization patterns, the allergen exposome—comprising environmental factors such as climate, urbanization, dietary habits, microbiota composition, and exposure to pollutants—plays a crucial role in shaping immune responses [14,15]. Geographic variability influences specific IgE (sIgE) profiles, potentially affecting the prevalence and severity of edible insect allergies across different populations. Regions with high, year-round exposure to HDM and storage mites may exhibit distinct sensitization patterns compared to areas where such exposure is less prevalent [16,17].

In this context, our study aims to characterize the molecular profile of individuals sensitized to EI despite no prior conscious exposure. Conducted within a subtropical region with persistent HDM and storage mite exposure, yet relatively low rates of intestinal parasitic infections and cockroach sensitization, this research seeks to clarify the clinical relevance of mite-related cross-reactivity and contribute to a broader understanding of emerging food allergies associated with entomophagy [18,19].

2. Materials and Methods

2.1. Subjects

Between March and September 2024, we conducted a retrospective analysis of consecutive patients attending the Outpatient Allergy Clinic, Immunotherapy, and Severe Asthma Unit at Hospital Universitario de Canarias in Tenerife, Spain. Eligible participants were required to exhibit IgE-mediated reactivity, as determined by a molecular allergen diagnostic platform, and have a clinical history suggestive of allergy-mediated disease. Sensitization to at least one insect extract—migratory locust (*Locusta migratoria*, Lm), house cricket (*Acheta domesticus*, Ad), or mealworm (*Tenebrio molitor*, Tm)—as detected through IgE microarray analysis, defined the study subgroup for data evaluation. This investigation received approval from the local Ethical Committee (approval code CHUC 2023 66). Written informed consent was obtained from all participants, with parental or guardian consent required for individuals under 18 years of age.

Clinical data were extracted from patients' medical records, including sociodemographic information, clinical history -encompassing past medical conditions and current allergy diagnoses-, and medication details. The severity and stage of allergic diseases were assessed following established guidelines [20,21]. Patients who had previously undergone or were currently receiving allergen immunotherapy or monoclonal antibody (biologic) treatment were excluded. Additionally, pregnant, and breastfeeding women were not included in the study.

2.2. Serological Analysis

Blood samples were collected from all participants, assigned unique identification codes, and stored at -40°C until analysis. Samples were thawed immediately before in vitro testing. Total and sIgE levels were measured using the ALEX²® MacroArray platform (MacroArray Diagnostics, Vienna, Austria) following the manufacturer's protocol. This multiplex assay includes 282 reagents, comprising 157 whole allergens—among them extracts from Ad, Lm, and Tm—as well as 125 molecular components. These allergens are immobilized on polystyrene nanobeads and deposited onto a nitrocellulose membrane, as previously described [22].

Total IgE levels were reported in international units per milliliter (IU/mL), while sIgE levels were expressed in kUA/L, with values ≥ 0.3 kUA/L considered positive. The assay included 17 molecular allergens derived from mites: Der p 1, Der p 2, Der p 5, Der p 7, Der p 10, Der p 11, Der p 20, Der p

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21, Der p 23, Der f 1, Der f 2, Blo t 5, Blo t 10, Blo t 21, Lep d 2, Gly d 2, and Tyr p 2. Additionally, the microarray incorporated panallergens classified according to their reactivity profiles.

Tropomyosin reactivity was defined by the presence of IgE antibodies targeting Ani s 3, Blo t 10, Der p 10, Pen m 1, or Per a 7. Sensitization to AK was identified through reactivity to at least one of the following molecules: Pen m 2, Bla g 9, or Der p 20. Further markers assessed included Pen m 3 (myosin light chain), Pen m 4 (sarcoplasmic calcium-binding protein), Cra c 6 (troponin C), and Der p 11 (paramyosin).

2.4. Statistical Analysis

Demographic characteristics were summarized using medians and standard deviations for continuous variables and percentages for categorical variables. Group differences were analyzed using appropriate statistical tests: Analysis of Variance (ANOVA) was applied to parametric continuous variables, while the Kruskal-Wallis and Mann-Whitney U tests were used for nonparametric continuous variables. Categorical variables were compared using the Chi-square test. Statistical significance was set at a P-value < 0.05. To assess allergen associations, simple logistic regression was performed, adjusting for potential confounding variables. All statistical analyses were conducted using GraphPad Prism version 10.0.0 (GraphPad Software, La Jolla, California, USA).

3. Results

3.1. Study Population

From March to September 2024, we conducted a proteomic analysis using the ALEX²® MacroArray platform on 634 consecutive patients. Sensitization was identified in 138 individuals (21.76%) to at least one EI extract: Lm, Ad, and/or Tm. Among the sensitized individuals, the majority (102/138) had a clinical history suggestive of food allergy, either alone or in combination with a respiratory condition such as allergic rhinitis and/or asthma, while the remaining 36/138 presented exclusively with allergic rhinitis and/or allergic asthma. Notably, males were disproportionately affected (68.84%), with a median age of 18 years (range: 3–75 years) (Figure 1 and Table 1).

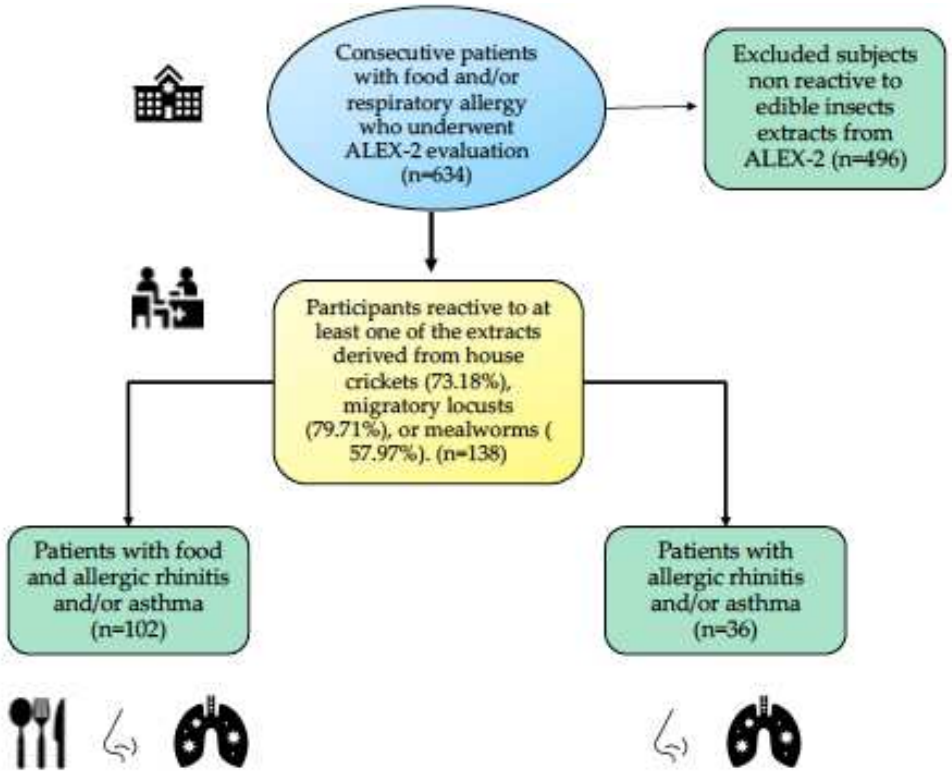

Figure 1. Flow diagram of patients and study selection. ALEX-2®: Allergy Explorer-2® MacroArray platform (MacroArray Diagnostics, Vienna, Austria) **.**

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Table 1. Demographic and clinical characterization data of investigated cohort.

Characteristics	(n=138)
Age (y.o.) median (range)	17 (3-75)
Sex (F/M)	43/95
Food and respiratory allergy	80
Food allergy	22
Seafood allergy	40
Respiratory allergy	36
Allergic rhinitis	21
Allergic rhinitis and asthma	15
Total IgE (IU/ml) median (range)	532 (54-2,500)
Family History of Atopy (%)	105 (77.08)

3.2. Specific IgE Profile in Pacients with a Sensitization to EI

Sensitization to at least one EI extract was identified in 138 individuals, with the following distribution: Lm in 110 individuals (79.71%), Ad in 101 (73.18%), and Tm in 80 (57.97%). Among the sensitized individuals, 65 (47.1%) exhibited concurrent sensitization to all three EI. Single-reactor cases were distributed as follows: Lm = 22 (15.94%), Ad = 19 (13.76%), and Tm = 8 (5.79%).

Tropomyosin emerged as the serodominant allergen (63.76%) in our cohort, followed by troponin-C (28.98%), AK (26.81%), and sarcoplasmic calcium-binding protein (8.69%). Additionally, 6.52% of subjects were sensitized to myosin light chain (Pen m 3), while only one individual (0.72%) displayed IgE reactivity to Der p 11 paramyosin (Table 2).

Table 2. Number (%) of selected patients (n=138) with a sensitization to edible insect/s and IgE reactivity to panallergens. Tropomyosin reactivity involves IgE antibodies to Ani s 3, Blo t 10, Der p 10, Pen m 1, or Per a 7. Arginine kinase sensitization is defined by reactivity to Pen m 2, Bla g 9, or Der p 20. Additional markers include Pen m 3 (myosin light chain), Pen m 4 (calcium-binding protein), Cra c 6 (troponin C), and Der p 11 (paramyosin). "None" indicates no IgE reactivity to any panallergens.

Panallergens in 138 subjects sensitized to at least one edible insect	***Acheta domesticus* (n=101)**	***Locusta migratoria* (n=110)**	***Tenebrio molitor* (n=80)**
Tropomyosin (any) molecules in 88/138 subjects (63.76%)			
Ani s 3 (n=76)	69 (68.31)	67 (60.9)	58 (72.5)
Blo t 10 (n=79)	71 (70.29)	68 (61.81)	62 (77.5)
Der p 10 (n=64)	62 (61.38)	58 (52.72)	57 (71.25)
Per a 7 (n=68)	64 (63.36)	60 (54.54)	58 (72.5)
Pen m 1 (n=63)	62 (61.38)	58 (52.72)	54 (67.5)
Arginine Kinase (any) molecules in 46/138 subjects (33.33%)			
Bla g 9 (n=36)	27 (26.73)	33 (30)	22 (27.5)
Der p 20 (n=39)	32 (31.68)	35 (31.81)	27 (33.75)
Pen m 2 (n=26)	23 (22.77)	25 (22.72)	23 (28.75)
Paramyosin Der p 11 in 1/138 subjects (0.72%)	1 (0.99)	1 (0.9)	1 (1.25)
Troponin-C Cra c 6 in 40/138 subjects (28.98%)	34 (33.66)	37 (33.63)	31 (76.25)
Myosin Light Chain Pen m 3 in 9/138 subjects (6.52%)	8 (7.92)	8 (7.27)	8 (10)
Sarcoplasmic Calcium Binding Protein Pen m 4 in 12/138 subjects (8.69%)	8 (7.92)	10 (9.09)	8 (10)
None (32/138 (23.18%) subjects)	24 (23.76)	22 (20)	10 (10)

Interestingly, 32 out of 138 individuals (23.18%) sensitized to EI showed no IgE reactivity to any of the panallergens—TM, AK, paramyosin, troponin C, and myosin light chain—on the ALEX2® chip. Additionally, only 4 of the 138 subjects (2.89%) sensitized to EI in our study exhibited no reactivity to any of the molecules included in the microarray panel.

3.3. Multiplex IgE Reactivity Profiles in Patients with Sensitization to EI and Exclusively Affected by Respiratory Allergy

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All 36 insect-reactive individuals (100%) diagnosed with allergic rhinitis and/or asthma, but not food allergies, were sensitized to at least one mite allergen. Eight allergens—Der f 2, Der p 23, Der p 2, Der p 1, Der f 1, Der p 5, Der p 7, and Blo t 21—were identified in over 50% of the cohort, making them serodominant. The majority of patients were cross-sensitized to group 2 mite allergens, specifically Der f 2 and Der p 2, with lesser cross-sensitization to Gly d 2, Tyr p 2, and Lep d 2. Sensitization to storage mite group 2 allergens was notably high, dominated by Gly d 2 (47.22%), followed by Tyr p 2 (41.66%) and Lep d 2 (36.11%). Remarkably, reactivity to panallergens was infrequent (5 out of 36 patients), with Der p 20 in 3 cases (8.33%), Der p 10 in 1 case (2.77%), and Blo t 10 in 1 case (2.77%). No cases of Der p 11 sensitization were observed (Table 3).

Table 3. Serological analysis of specific IgE (sIgE) responses (kU/L) to 17 mite molecular allergens in selected patients (n=36) with a sensitization to at least one edible insect and concomitant respiratory allergy -i.e., allergic rhinitis, or allergic rhinitis and asthma- excluding food allergy. The number (%) of subjects (n=36) sensitized to the corresponding mite molecular allergen is shown.

Mite allergen	Mean sIgE (M±SD)	No. of sensitized patients (%)
Der f 2	20.64±16.33	32 (88.88)
Der p 2	22.75±15.75	31 (86.11)
Der p 1	17.51±15.38	30 (83.33)
Der p 23	17.77±15.67	28 (77.77)
Der f 1	10.72±12.42	25 (69.44)
Der p 5	15.2±16.25	22 (61.11)
Der p 7	18.89±16.35	21 (58.33)
Blo t 21	12.91±13.11	19 (52.77)
Gly d 2	3.8±3.92	17 (47.22)
Tyr p 2	4.66±5,99	15 (41.66)
Der p 21	17.22±20.32	14 (38.88)
Blo t 5	11.09±13.11	14 (38.88)
Lep d 2	3.2±2.95	13 (36.11)
Der p 20	1.4±1.75	3 (8.33)
Der p 10	0.23±0.18	1 (2.77)
Blo t 10	0.24±0.09	2 (5.55)
Der p 11	<0.35	0 (0)

3.4. Allergen-Specific IgE Levels to TMs, AKs, and Different EI Extracts Were Significantly Correlated

In the investigated cohort, only 6 out of 138 individuals (4.34%) sensitized to EI showed no reactivity to any of the 17 mite allergens tested, which included Der p 1, Der p 2, Der p 5, Der p 7, Der p 10, Der p 11, Der p 20, Der p 21, Der p 23, Der f 1, Der f 2, Blo t 5, Blo t 10, Blo t 21, Lep d 2, Gly d 2, and Tyr p 2. Among these 17 mite-derived molecules, significant ($p < 0.05$) correlations with sensitization to EI were found only for two allergen groups: AK with Der p 20 ($r = 0.26$) and TM with Blo t 10 ($r = 0.78$) and Der p 10 ($r = 0.86$).

4. Discussion

The increasing use of EI as a sustainable protein source has raised concerns about their allergenic potential [23,24]. Mite-EI syndrome exemplifies a complex interplay between insects, mites, and their environments, particularly in subtropical regions with high mite prevalence. This syndrome, a subset of the broader dust mite–crustacean–insect syndrome, underscores the significant cross-reactivity among these arthropods, often affecting individuals sensitized to mites who subsequently develop allergies to crustaceans and EI [25,26]. Understanding these immune mechanisms provides valuable insights into allergen cross-reactivity beyond single food sources. Lipid transfer protein (LTP) syndrome, a leading cause of plant-derived food allergies, provides a useful parallel [27,28]. LTPs, as stable pan-allergens found in various plant species, often initiate sensitization through inhalant exposure before progressing to food allergies. Similarly, we hypothesize that in mite-prevalent regions, inhalant exposure to either HDM or storage mites may serve as an initial trigger for EI sensitization, even in individuals without prior direct exposure. Former research has demonstrated that shrimp

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allergy can be strictly dependent on HDM sensitization, a pattern that may extend to EI allergy in certain geographic areas [29,30].

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4.1. Molecular Sensitization Patterns in the Investigated Cohort

In our study, TM was the most prevalent allergen (63.76%), followed by troponin-C (28.98%), AK (26.81%), and sarcoplasmic calcium-binding protein (8.69%) [31,32]. A smaller proportion (6.52%) were sensitized to myosin light chain (Pen m 3), and only one individual (0.72%) reacted to Der p 11 paramyosin. Notably, 23.18% of participants exhibited no IgE reactivity to the pan-allergens on the ALEX2® chip. This contrasts with a Mediterranean cohort where 55.4% of insect-reactive individuals lacked pan-allergen sensitization, suggesting possible regional variations in sensitization profiles [33]. Interestingly, a subset of four participants in our cohort displayed specific IgE to EI but no reactivity to other food or inhalant allergens, suggesting that EI may serve as a primary sensitizer in some individuals. These findings highlight the potential for EI to be an independent cause of allergic sensitization, rather than solely a result of cross-reactivity.

4.2. Cross-Reactivity Among EI and Other Allergens

Our study confirms clinically relevant cross-reactivity between EI and crustaceans, driven by pan-allergens such as TM, troponin-C, and AK. However, the relationship between mite and EI sensitization remains debated. Previous research suggested an inverse correlation between mite sensitization and IgE reactivity to EI, implying mites might not act as primary sensitizers [33,34]. Our findings challenge this assumption, showing that 95.66% of individuals sensitized to EI also reacted to at least one of the 17 investigated mite allergens, with significant correlations ($p < 0.05$) between EI sensitization and key molecular pan-allergens. In this regard, despite former research has shown that individuals with HDM allergies may experience allergic reactions after consuming EI, the clinical relevance of co-sensitization to mites and EI is still debated, with more studies required to understand the mechanisms of allergic responses. Despite epidemiological data on allergic reactions to EI among patients with mite allergies is scarce, in a recent study of 6,173 individuals, 4.3% showed sensitization to yellow mealworm, with a notable association between this sensitization and HDM allergies [35]. In our cohort, among the 36 EI-reactive individuals diagnosed exclusively with allergic rhinitis and/or asthma (without food allergies), all were sensitized to at least one mite molecule. However, they exhibited infrequent reactivity to pan-allergens such as Der p 20 (8.33%), Der p 10 (2.77%), and Blo t 10 (2.77%). These findings suggest that while HDM exposure may contribute to EI sensitization, its exact role requires further investigation.

4.3. Insect-Specific Proteins and Sensitization Mechanisms

While cross-reactivity explains some EI sensitization cases, the presence of insect-specific proteins such as chemosensory proteins (CSP), odorant-binding proteins (OBP), and hexamerin suggests alternative sensitization pathways [36,37]. These proteins, largely absent in phylogenetically related organisms such as mites and crustaceans, may contribute independently to EI sensitization. The precise immunological mechanisms remain unclear and warrant further research.

4.4. Limitations

Diagnosing mite-EI syndrome is challenging due to overlapping allergens among mites, crustaceans, and EI [38,39]. Although component-resolved diagnostics could help distinguish primary sensitization from cross-reactivity, their limited availability restricts precise assessments. Moreover, treatment options for this syndrome remain limited, with management largely focused on avoidance and emergency preparedness in case of anaphylaxis [40–42]. A major limitation of our study was the absence of clinical food challenges, which are crucial for assessing the clinical significance of insect-specific sensitization patterns. While food challenges have been used successfully in shrimp-allergic patients, particularly those co-sensitized to specific pan-allergens, similar investigations in mite-allergic populations are lacking [43–45]. Furthermore, the sample size of our cohort limits the generalizability of our findings.

5. Future Perspective and Conclusions

Despite the growing recognition of the allergenic potential of edible insects, further research is urgently needed to clarify the clinical relevance of cross-reactivity between mites, crustaceans, and EI. Public health policies should prioritize addressing the risks of allergic reactions to edible insects, particularly among individuals with known mite or shellfish allergies [46,47]. Regulatory

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frameworks should continue to include allergen labeling, consumer education, and further research into strategies for reducing the allergenicity of edible insects.

This investigation highlights regional variations in molecular sensitization profiles among individuals reactive to EI. In subtropical regions, increased mite exposure appears to influence IgE responses to insect proteins, emphasizing the complex interplay between environmental factors and allergen cross-reactivity and suggesting that food sensitization is shaped by multiple determinants. Although the lack of specific food challenge data limits the clinical assessment of insect-specific sensitization in mite-allergic individuals, these findings indicate that EI sensitization should be recognized as a distinct immunological concern rather than an incidental phenomenon.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the local Institutional Ethics Committee CEIC Hospital Universitario de Canarias, Tenerife, Spain on 2023 October, 26 (reference number CHUC_2023_66) for studies involving humans.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from Servicio Canario de Salud but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Servicio Canario de Salud.

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Abbreviations

The following abbreviations are used in this manuscript:

Tm	*Tenebrio molitor*
EI	Edible Insects
EFSA	European Food Safety Authority
HDM	House Dust Mites
TM	Tropomyosin
Lm	*Locusta migratoria*
Ad	*Acheta domesticus*
AK	Arginine Kinase

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