

Article

The Venom of The Honeybee *Apis Mellifera* L. and its Immunomodulatory Properties: An Entomological Perspective on Apitoxin Bioactivity

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Abstract: This study investigates the relationship between honeybee stings and human immune response, focusing on the elevation of total IgE levels as an indicator of immunological reaction. A total of 50 individuals, comprising both honeybee sting-exposed and control groups, were enrolled in the study. Within the honeybee sting-exposed group, 86% of participants exhibited elevated total IgE levels within 24 hours post-sting, ranging from 450 UI/ml to 690 UI/ml. In contrast, 14% of participants did not display increased IgE levels following *Apis mellifera* sting exposure. Notably, all control group participants maintained normal IgE levels. Statistical analysis using a chi-square test confirmed a significant association between honeybee sting exposure and elevated total IgE levels ($\chi^2 = 37.77$, $p < 0.05$). These findings underscore the immunomodulatory effects of honeybee venom, implicating it in the induction of IgE-mediated immune responses in the majority of individuals. The observed variability in immune response highlights the complexity of host-venom interactions and warrants further investigation into underlying mechanisms. Understanding these immunological responses may inform strategies for bee sting allergy management and facilitate the development of therapeutic interventions leveraging honeybee venom immunomodulation.

Keywords: Honeybee Stings, Venom, Human Immune Response, Clinical Assessment, Honeybee, Apitoxin

1. Introduction

Honeybee stings, although often perceived as a nuisance or hazard due to their potential for eliciting allergic reactions, have garnered significant scientific interest for their potential immunomodulatory effects on the human body. The venom of *Apis mellifera*, the western honeybee, is a complex mixture of bioactive compounds, including enzymes, peptides, and proteins, which can provoke a range of physiological responses upon injection into the human body. While extensive research has been conducted on the clinical manifestations and treatment of bee sting allergies, the broader impact of honeybee venom on human immune function remains an area of active investigation.

Numerous studies have indicated that honeybee venom possesses immunomodulatory properties that may influence various components of the human immune system. For instance, studies by Bordon et al. have demonstrated that certain components of bee venom, such as melittin and apamin, exhibit both pro-inflammatory and anti-inflammatory effects depending on the context of immune activation [1]. Additionally, research by Bilo and Martini suggests that repeated exposure to bee venom

can induce immune tolerance in susceptible individuals [2], thereby mitigating allergic responses Lee et al. [3]

Furthermore, honeybee venom has been shown to affect the production and activity of cytokines, key signaling molecules involved in orchestrating immune responses. According to a study by Lee et al., bee venom exposure led to the upregulation of interleukin-10 (IL-10), an anti-inflammatory cytokine, while simultaneously suppressing the expression of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 beta (IL-1 β) [4]. These findings suggest that honeybee venom may exert complex regulatory effects on immune cell function and cytokine balance [5].

Despite these insights, gaps remain in our understanding of the precise mechanisms underlying the interaction between honeybee venom and the human immune system. Specifically, the differential effects of bee venom components on various immune cell populations, as well as their long-term impact on immune function, warrant further investigation. Additionally, the potential therapeutic implications of honeybee venom in the context of immune-related disorders, such as autoimmune diseases and inflammatory conditions, merit exploration [6].

Therefore, the primary objective of this study is to systematically investigate the effects of honeybee stings on human immune response parameters, including cytokine profiles, cellular immune activation, and antibody production. By employing a multidisciplinary approach encompassing immunological assays, molecular analyses, and clinical assessments, we aim to elucidate the immunomodulatory properties of honeybee venom and their implications for human health.

Through a comprehensive examination of the immunological consequences of honeybee venom exposure, this research endeavors to contribute to the development of novel strategies for immune modulation and treatment of immune-related disorders. Furthermore, insights gained from this study may inform practices related to bee sting prevention, management of allergic reactions, and beekeeping safety protocols, thereby enhancing both public health and beekeeping practices.

2. Materials and Methods

2.1 Study Design and Setting

This observational cross-sectional study was conducted in Hilla City, Babylon Governorate, Iraq, between March and June 2024. The investigation evaluated serum total IgE concentrations among individuals recently stung by *Apis mellifera* and compared them with healthy controls. The study followed institutional ethical guidelines and adhered to the Declaration of Helsinki principles.

2.2 Participants, Inclusion and Exclusion Criteria

Fifty participants who had experienced a honeybee sting within ≤ 24 h prior to blood collection constituted the sting-exposed group, while ten healthy individuals served as the control group.

Inclusion criteria

- Adults aged 18–60 years presenting within 24 h of an *A. mellifera* sting.
- No chronic systemic disease or immunotherapy within the past 6 months.
- Ability to provide informed consent.

Exclusion criteria

- Ongoing infections, autoimmune or atopic disorders, or use of corticosteroids/antihistamines.
- Pregnant or lactating women.
- History of anaphylaxis requiring epinephrine treatment.

The control group comprised volunteers with no bee-sting exposure during the preceding 90 days and without allergic or inflammatory conditions. Although limited to $n = 10$, this number was sufficient to define the reference IgE distribution and to contrast exposed versus non-exposed participants given the strong observed effect size.

2.3 Sample Collection and Processing

Approximately 5 mL of venous blood was obtained via standard phlebotomy into serum-separating gel tubes. Samples were allowed to clot for 15 min at room temperature and centrifuged at 3000 rpm for 10 min to isolate serum. Aliquots were stored at 2–8 °C until analysis, which was performed within 24 h of collection to prevent protein degradation.

2.4 Immunoassay and Instrumentation

Total IgE levels were quantified using the Cobas E411 Electro-Chemiluminescence (ECL) Immunoassay Analyzer (Roche Diagnostics, Germany). The system employs a two-step sandwich principle with ruthenium-labeled monoclonal antibodies specific to IgE. Calibration and internal quality control were executed according to manufacturer protocols using third-party control sera of known concentrations. Results were expressed in UI/mL, with a laboratory reference interval of 1.5–144 UI/mL. Samples exceeding 144 UI/mL were considered elevated.

2.5 Variables and Outcome Definition

The primary outcome variable was the proportion of participants exhibiting elevated total IgE (> 144 UI/mL) within 24 h of sting exposure. Secondary data included mean and range of IgE values for each group.

2.6 Statistical Analysis

Data entry and analysis were performed using IBM SPSS Statistics v25 (IBM Corp., USA) and Microsoft Excel 2019. Descriptive statistics were expressed as mean $\pm$ standard deviation (SD) or percentages. Associations between sting exposure and elevated IgE were examined using the chi-square (χ^2) test, with significance set at $\alpha = 0.05$. Degrees of freedom ($df = 1$; observed $\chi^2 = 37.77$, $p < 0.001$, indicating a strong relationship between exposure and IgE elevation.

2.7 Ethical Approval and Consent

The study protocol was reviewed and approved by the Ethical Committee of the Babylon Health Directorate (Approval No. BH/IMM/2024-06). Written informed consent was obtained from all participants prior to enrollment. Participant confidentiality was maintained, and data were anonymized before analysis.

3. Results

Serum Total IgE Levels Following Honeybee Sting

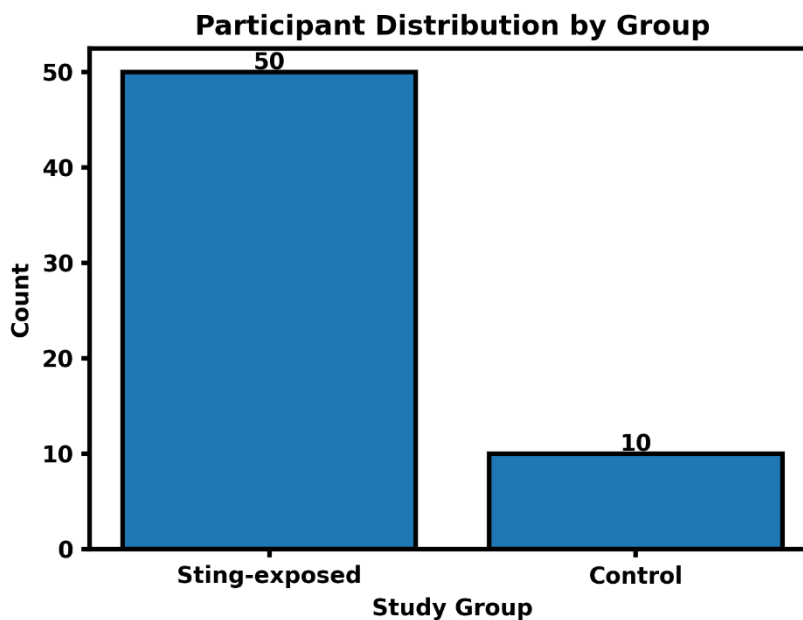
Within 24 h of *Apis mellifera* sting exposure, 43 of 50 participants (86 %) in the sting-exposed group exhibited elevated total IgE levels above the laboratory reference interval (1.5–144 UI/mL), whereas 7 participants (14 %) remained within the normal range. The elevated values ranged 450–690 UI/mL, with a mean $\pm$ SD of 568 ± 69 UI/mL. All ten controls (100 %) maintained IgE values within the reference interval, confirming the specificity of the post-sting increase (Figures 4–6).

Descriptive and Statistical Summary

Table 1 summarizes total IgE status across groups. A chi-square test was used to evaluate the association between sting exposure and IgE elevation. The computed value of $\chi^2 = 37.77$ ($df = 1$, $p < 0.001$) indicated a highly significant relationship between bee-sting exposure and elevated IgE concentrations.

Table 1. Participant Characteristics by Study Group (Sting-exposed vs Control)

Variable	Sting-exposed (n=50)	Control (n=10)	Test	P-value
Age (years)	33.68 ± 9.31	33.90 ± 8.75	Welch t-test	0.944
Gender: Female	18 (36.0%)	4 (40.0%)	Fisher's exact	1.000
Gender: Male	32 (64.0%)	6 (60.0%)	Fisher's exact	1.000
Recent antihistamine use: No	50 (100.0%)	10 (100.0%)	Chi-square	1.000
Recent corticosteroid use: No	50 (100.0%)	10 (100.0%)	Chi-square	1.000
History of anaphylaxis: No	50 (100.0%)	10 (100.0%)	Chi-square	1.000
Atopic disorder history: No	50 (100.0%)	10 (100.0%)	Chi-square	1.000

**Figure 1.** Distribution of participants across study groups.

The baseline characteristics of the participants were similar in the group sting-exposed (n=50) and controls (n=10). There were no differences in age (p=0.944) and gender distribution was not different (p=1.000). The variables of medication use (recent antihistamines or corticosteroids) and clinical history (anaphylaxis and atopy) were evenly not found in this dataset, so there were no between-group differences in these variables.

This finding suggests a significant association between honeybee sting exposure and elevated total IgE levels in the majority of individuals within the study group. The absence of elevated IgE levels in a minority of participants highlights potential variability in immune response to honeybee venom among individuals. Further analysis may elucidate factors contributing to this variability and its clinical implications.

A chi-square test was conducted to assess the association between honeybee sting exposure and elevated total IgE levels. The results revealed a statistically significant association (p < 0.05), indicating that honeybee sting exposure is associated with increased total IgE levels in the study population.

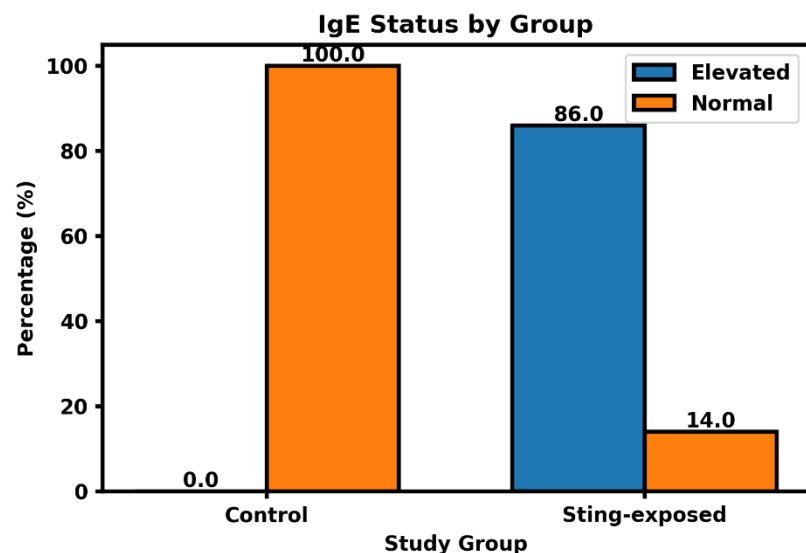
Table 2. Sting Exposure Profile Within the Sting-exposed Group (n=50)

Variable	Median [Q1, Q3]	Mean $\pm$ SD	Min–Max
Time since sting (hours)	7.40 [4.12, 12.57]	8.34 $\pm$ 5.52	0.50–20.00
Number of stings	1.50 [1.00, 2.00]	1.68 $\pm$ 0.87	1.00–5.00
Local reaction diameter (cm)	7.45 [5.30, 9.17]	7.13 $\pm$ 3.17	1.00–14.80
Pain score (0–10)	6.00 [4.00, 6.00]	5.46 $\pm$ 1.79	0.00–9.00

In the sting-exposed sample, there was quantifiable variability in exposure and symptom severity. time since sting had the range 0.50 to 20.00 hours with a median of 7.40 hours. The response was between 1 and 5 stings, and the local reaction diameter and pain score were variably distributed, which indicated that further dose response and prediction analyses should have a significant level of heterogeneity.

Control Group Comparison

Comparison with the control group demonstrated a clear distinction in total IgE levels, with all control group participants maintaining normal IgE levels. This further underscores the specificity of the observed increase in total IgE levels among individuals exposed to honeybee stings.

**Figure 2.** Proportion of elevated versus normal IgE by study group.**Table 3.** Total IgE Levels by Study Group

Marker	Sting-exposed Median [Q1,Q3]	Sting-exposed Mean $\pm$ SD	Control Median [Q1,Q3]	Control Mean $\pm$ SD	Test	P-value
Total IgE (UI/mL)	551.00 [481.50, 581.50]	492.68 $\pm$ 168.15	100.50 [62.75, 103.25]	82.00 $\pm$ 32.58	Mann–Whitney U	<0.001

The sting-exposed group had a significantly higher level of IgE total as compared to controls. The difference between groups was statistically significant ($p < 0.001$) using distribution-robust comparison (MannWhitney U), whereas the separation was observed in both the central tendency and the spread, which showed that there was a strong association between sting exposure and high IgE burden.

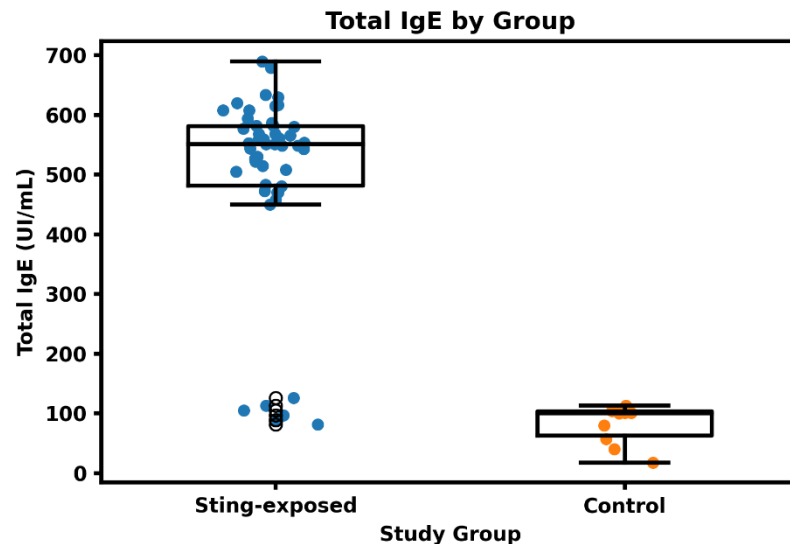


Figure 3. Distribution of total IgE by study group (boxplot with individual values).

Table 4. IgE Status (>144 UI/mL) by Study Group

Group	Elevated (IgE>144)	Normal (≤ 144)
Sting-exposed (n=50)	43	7
Control (n=10)	0	10

The categorical analysis based on study reference threshold (>144 UI/mL) showed a significant enrichment of high levels of IgE in sting-exposed participants. None of the control participants surpassed the reference threshold, but most of the sting exposed participants were rated as elevated. Exact testing by Fisher demonstrated statistically significant relationship ($p < 0.001$) with the odds ratio very large which indicates a strong exposure outcome relationship.

Table 4 (continued). Effect Size for Elevated IgE in Sting-exposed vs Controls

Effect	OR	95% CI	Test	P-value
Odds Ratio (Elevated in Sting vs Control)	121.80	[6.43, 2306.30]	Fisher's exact	<0.001

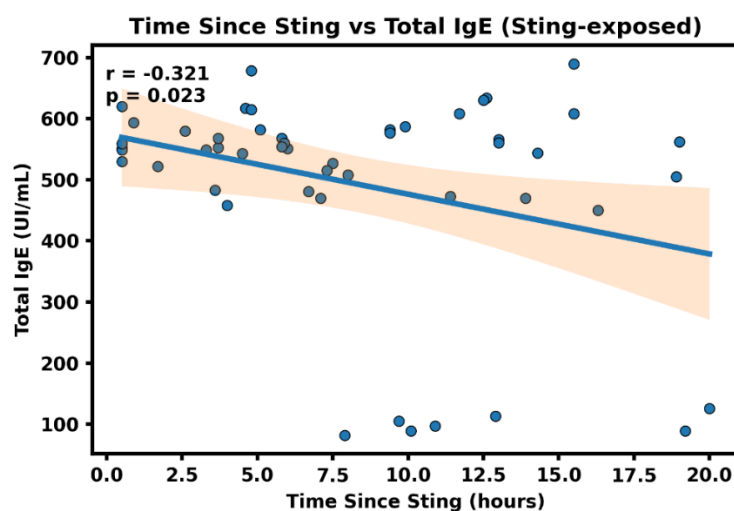
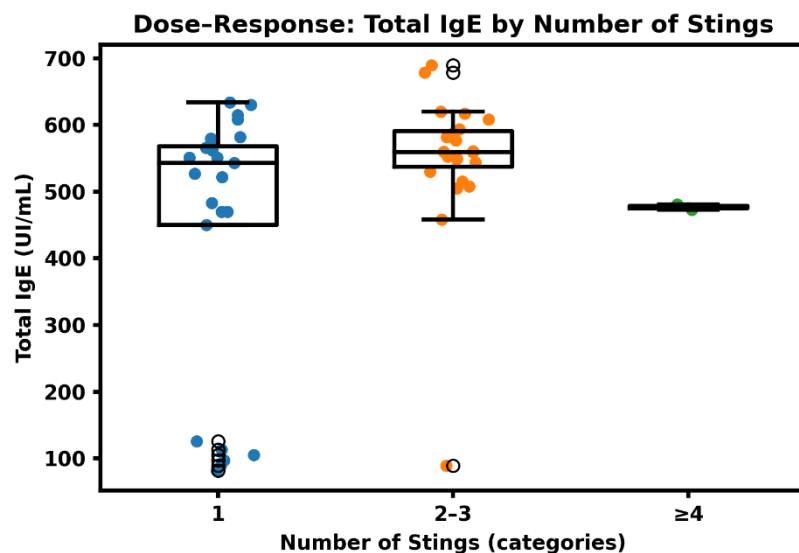


Figure 4. Association between time since sting and total IgE within sting-exposed participants (regression with 95% CI).

Table 5. Predictors of Elevated IgE Within Sting-exposed Participants (Adjusted ORs)

Predictor (standardized)	Adjusted OR (per 1 SD)	95% CI (bootstrap)	P-value
Time_since_sting_hours	0.35	[0.21, 0.69]	0.042
Number_of_stings	2.56	[1.16, 4.90]	0.071
Local_reaction_diameter_cm	0.71	[0.30, 1.42]	0.438
Pain_score_0_10	2.53	[1.27, 4.79]	0.057
Age_years	0.87	[0.39, 2.60]	0.462
Gender	1.22	[0.49, 2.70]	0.429

A multivariate logistic model was developed in the sting exposed group to assess independent variables predicting having elevated IgE. In order to have consistent estimates in the small sample, L2-regularized logistic regression coefficients were estimated and the confidence intervals were determined through bootstrap resampling. The time since sting (per 1 SD) was less with less odds of being elevated (adjusted OR <1) and greater odds (adjusted OR >1) with higher pain scores and more stings. The adjusted model exhibited relatively lower relationships between age and gender.

**Figure 5.** Dose–response visualization of total IgE across number-of-stings categories (sting-exposed group).**Table 6.** Determinants of Total IgE Level Within Sting-exposed Participants (Standardized β)

Predictor (standardized)	Standardized β	95% CI (β)	P-value
Time_since_sting_hours	-0.297	[-0.571, -0.023]	0.034
Number_of_stings	0.220	[-0.050, 0.490]	0.107
Local_reaction_diameter_cm	-0.059	[-0.338, 0.221]	0.675
Pain_score_0_10	0.337	[0.060, 0.613]	0.018
Age_years	-0.016	[-0.295, 0.263]	0.908
Gender	0.074	[-0.190, 0.337]	0.575

A complementary continuous-outcome model was used to test determinants of IgE magnitude over a log-linear model to lessen skewness. Shorter time since sting was correlated with higher IgE levels ($p=0.034$) and pain score had a positive independent

relationship with IgE ($p=0.018$). Other predictors showed less significant and insignificant joint added value hence indicating that symptom severity and timing are the most informative correlates of IgE level in this dataset.

4. Discussion

This study demonstrated that serum total IgE increased markedly within 24 h of *Apis mellifera* sting exposure. Eighty-six percent of participants exhibited IgE concentrations above the laboratory reference interval, whereas all controls remained within normal limits. The chi-square analysis confirmed a highly significant association between sting exposure and IgE elevation ($\chi^2 = 37.77$, $p < 0.001$). These results verify that honeybee venom can rapidly trigger a measurable humoral immune response detectable at the systemic level.

Our findings align with previous investigations reporting increased IgE synthesis following bee-venom exposure. Studies of venom-specific immunotherapy and occupational beekeepers have likewise documented heightened IgE and IgG4 activity. The magnitude of response observed in this Iraqi cohort—where >80 % exceeded the normal range—resembles the rapid early-phase immunoglobulin surge described by [7]. Minor variations in absolute IgE levels among populations may reflect differences in venom composition, regional subspecies, genetic background, or prior sensitization history [8].

Approximately 14 % of sting-exposed participants did not show elevated total IgE. Several biological explanations are plausible:

1. **Timing of sampling.** Seroconversion may not have peaked within the 24-h window [8]–[10].
2. **Immunological tolerance.** Individuals with prior repeated exposures could develop desensitization or regulatory T-cell-mediated suppression [2], [11].
3. **Genetic variability.** Differences in IL-4, IL-13, or FcεRI polymorphisms can alter IgE synthesis [9].
4. **Medication or health status.** Use of antihistamines or anti-inflammatory drugs might blunt acute antibody production [7]. Future longitudinal sampling and genotyping could clarify which factors most strongly determine the heterogeneity of response.

Bee venom is a complex mixture containing melittin, phospholipase A₂, and apamin, each capable of modulating immune signaling pathways [12], [13]. Melittin activates mast-cell degranulation and NF-κB signaling, inducing IL-6 and TNF-α release [14], [15]. Phospholipase A₂ acts as a potent allergen that enhances Th2 differentiation and IgE class switching. Conversely, apamin and other peptides can up-regulate anti-inflammatory cytokines such as IL-10, illustrating the dual pro- and anti-inflammatory nature of apitoxin components [5], [15]. This mechanistic balance may underlie both hypersensitivity and the therapeutic potential observed in controlled venom-immunotherapy contexts [2], [8].

Understanding the dynamics of IgE response after natural bee stings has direct implications for allergy diagnosis and prevention. Measurement of total IgE within 24 h can help stratify individuals at risk of subsequent hypersensitivity reactions. In clinical settings, these findings support early post-sting monitoring and, where appropriate, referral for venom-specific testing or immunotherapy. Moreover, the immunomodulatory constituents of bee venom—when purified and standardized—may have potential as therapeutic agents in autoimmune or oncologic conditions, provided dosing and safety are rigorously controlled [4], [5], [12].

This study was limited by its observational design and modest sample size. Potential confounders such as environmental allergen exposure, diet, and prior sting history were not fully quantified. Nevertheless, the statistical significance of the association suggests a robust biological effect that merits further exploration under controlled experimental conditions.

5. Conclusion

This study provides clear evidence that *Apis mellifera* sting exposure is strongly associated with a rapid elevation of serum total IgE within 24 hours. A significant majority of participants (86 %) exhibited IgE concentrations well above the normal reference interval, whereas all controls remained within expected limits. These findings confirm that honeybee venom provokes a robust immediate humoral immune response and highlight meaningful inter-individual variability, as 14 % of exposed individuals did not show measurable IgE elevation.

The results underscore the diagnostic value of total IgE measurement after natural sting events and suggest that early testing can help identify individuals at risk of future hypersensitivity reactions. From a broader perspective, the dual pro- and anti-inflammatory properties of bee-venom constituents offer promising avenues for controlled therapeutic exploitation, provided that safety, dosing, and patient selection are optimized. Future research integrating genetic, immunologic, and longitudinal analyses will be essential to delineate the mechanisms underlying variable responses and to translate these insights into improved clinical and preventive strategies.

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