

ORIGINAL ARTICLE

Comparative evaluation of Soluprick, skin prick testing and intradermal testing in *Apis mellifera* and *Vespula species* venom allergy: a multicenter real-life study

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Summary

Background. Skin testing is a cornerstone of the diagnostic work-up of Hymenoptera venom allergy. However, evidence comparing high-concentration venom prick testing (Soluprick 300 µg/mL) with others skin prick testing (SPT) and intradermal testing (IDT) remains limited. **Methods.** In this multicenter retrospective study, 123 consecutive adult patients evaluated for Hymenoptera venom allergy at three tertiary allergy centers were included. Skin test responses to *Apis mellifera* and *Vespula* spp. venoms were assessed using Soluprick 300 µg/mL, SPT (100 µg/mL), and IDT (0.1 and 1 µg/mL). Agreement between methods was assessed using concordance correlation coefficients and Bland-Altman plots, while systematic differences were evaluated using paired Wilcoxon signed-rank tests. **Results.** A total of 123 patients were included, of whom 32 (26.0%) were receiving venom immunotherapy. For *Apis mellifera* venom extract, Soluprick showed good comparability with conventional SPT 100 µg/mL (CC = 0.77). In contrast, concordance between Soluprick and IDT was poor, with significant systematic bias and significant paired differences ($p < 0.001$). For *Vespula* spp. venom extract, agreement between Soluprick and all alternative methods (including conventional SPT and IDT) was low. In addition, no significant differences in skin test responses were observed according to VIT status. **Conclusions.** Soluprick cannot be considered interchangeable with IDT. While it showed good comparability with conventional SPT 100 µg/mL for *Apis mellifera* venom, agreement was substantially lower for *Vespula* spp. These findings suggest that Soluprick should not be considered interchangeable with IDT in routine clinical practice.

IMPACT STATEMENT

Soluprick 300 µg/mL was not interchangeable with intradermal testing at 0.1 µg/mL, whereas a good comparability with skin prick testing 100 µg/mL was observed only for *Apis mellifera* venom extract.

Key words

Hymenoptera venom allergy; Soluprick; skin prick test; intradermal test; diagnostic testing.

Introduction

Hymenoptera venom allergy is one of the recognized causes of anaphylaxis in adults, which can be potentially life-threatening (1). Accurate diagnosis work-up is therefore crucial to identify patients eligible for venom immunotherapy (VIT), currently considered the only disease-modifying treatment able to prevent further systemic sting reactions. Current European Guidelines and Italian Consensus criteria recommend combining clinical history with the demonstration of Immunoglobulin (Ig)E-mediated sensitization through skin testing and/or serum specific IgE assessment (2,3). Moreover, recent diagnostic algorithms increasingly integrate component-resolved diagnostics (CRD), basophil activation testing (BAT), Cap-inhibition test and molecular biomarkers to improve discrimination between true sensitization and cross-reactivity (4-7). Furthermore, for risk stratification and to investigate a potential underlying mast cell disorder, baseline serum tryptase measurement is recommended in all patients with a history of severe systemic reactions (8). Venom skin testing remains a cornerstone of the diagnostic work-up of Hymenoptera venom allergy and traditionally includes both skin prick testing (SPT) and intradermal testing (IDT), representing, together with a thorough clinical history, identification of the culprit insect, and venom-specific IgE testing, a fundamental tool for selecting the appropriate VIT. According to current recommendations, SPT is usually performed using venom concentrations ranging from 10 to 100 µg/mL, whereas IDT is carried out with lower concentrations (0.001–1 µg/mL) (2,3,8). In clinical practice, however, most allergy centres routinely perform venom SPT at 100 µg/mL and IDT at 0.1 and 1 µg/mL as the standard diagnostic approach. Moreover, in several allergy centres, high-concentration prick preparations such as Soluprick 300 µg/mL are used in routine practice as a pragmatic alternative to IDT at 0.1 µg/mL, with the aim of reducing patient discomfort and simplifying diagnostic workflows, despite the limited evidence currently available in the literature supporting this approach. In parallel, recent advances in molecular allergology have significantly improved the characterization of Hymenoptera venom sensitization profiles; however, skin testing still represents a fundamental diagnostic tool because in vivo reactivity does not always correlate with serum biomarkers alone (2,3,9). Despite the widespread use of venom skin testing in routine allergy practice, direct comparative evidence between Soluprick 300 µg/mL and IDT 0.1 µg/mL remains extremely limited. Most available studies were conducted decades ago using heterogeneous venom extracts and protocols that are not directly comparable with contemporary diagnostic approaches (10-12). Besides the historical study by Jeep et al. (13), only a small number of investigations have specifically evaluated venom SPT at 300 µg/mL. In a French routine-practice study, SPT performed at 300 µg/mL showed substantially higher sensitivity compared with conventional 100 µg/mL testing for both honeybee and vespula venom allergy, leading the authors to conclude that venom concentrations below 300 µg/mL may be insufficient for optimal diagnostic sensitivity (11). In recent years, the introduction of high-concentration prick preparations such as Soluprick 300 µg/mL has renewed interest in the possible role of SPT as a simpler and less invasive alternative to IDT. Contemporary reviews and expert position papers have highlighted the need for more standardized and clinically applicable diagnostic strategies in Hymenoptera venom allergy, particularly in real-world settings (5,6,8). Nevertheless, contemporary real-world evidence on high-concentration venom SPT remains scarce and comparative multicentre studies evaluating its agreement with IDT in routine clinical practice are currently lacking. Consequently, despite its increasing pragmatic use in several Italian allergy centres as a less invasive alternative to IDT, the diagnostic role of Soluprick 300 µg/mL remains insufficiently characterized. The aim of this multicentre real-life study was to compare the results and concordance of conventional SPT, Soluprick, and IDT in the real-world diagnostic work-up of *Apis mellifera* and *Vespula spp.* venom allergy.

Materials and Methods

Study design and population

This retrospective multicentre real-life study was conducted in three tertiary referral allergy centres in Milan, Italy: Allergy and Clinical Immunology Unit at L. Sacco Hospital, SC Allergologia e Immunologia Clinica at ASST Grande Ospedale Metropolitano Niguarda and Allergy Clinic of

the Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico. A total of 123 consecutive adult (≥ 18 -year-old) patients referred during routine clinical practice for diagnostic evaluation of suspected Hymenoptera venom allergy following systemic reactions to Hymenoptera stings, according to the Mueller grading system (14), were retrospectively included. Demographic and clinical data were collected from medical records, including age, sex, atopic status, chronic urticaria, mastocytosis, total IgE levels, and ongoing VIT.

Skin testing

All patients underwent venom skin testing as part of routine clinical practice using commercially available venom extracts. Skin testing was performed for *Apis mellifera*, *Vespula spp.*, *Polistes dominula*, *Vespa crabro*. For the purpose of the present study, only results obtained with *Apis mellifera* and *Vespula spp.* venom extracts were included in the analysis, as high-concentration skin prick testing with Soluprick 300 $\mu\text{g/mL}$ was available exclusively for these venoms. Diagnostic work-up for *Apis mellifera* and *Vespula spp.* venom extract included: SPT at 100 $\mu\text{g/mL}$ (Allergy Therapeutics, West Sussex, UK), high-concentration SPT using Soluprick® SQ 300 $\mu\text{g/mL}$ (ALK-Abelló, Hørsholm, Denmark), and IDT at 0.1 and 1 $\mu\text{g/mL}$ (Allergy Therapeutics, West Sussex, UK). All diagnostic extracts were used in accordance with the manufacturer's instructions. Skin tests were performed on the volar surface of the forearm according to EAACI Guidelines and Italian Consensus criteria, at least two weeks after the culprit sting reaction. Histamine and saline solution (Lofarma S.p.A., Milan, Italy) were used as positive and negative controls, respectively, and skin reactions were evaluated after 15–20 minutes (2,3). Allergen-specific IgE antibodies to whole venom extracts and individual molecular components were quantified using the ImmunoCAP™ system (Thermo Fisher Scientific, Uppsala, Sweden), according to the manufacturer's instructions, as part of clinical practise. These serological results were not considered in the present analysis, which specifically focused on the comparison of skin reactivity among the different skin testing methods.

Statistical analysis

Wheal area was estimated as an ellipse from the two perpendicular wheal diameters. Data are presented as counts (and percentages, %) and mean (and standard deviation, SD) or median (and interquartile range, IQR), as appropriate. Baseline sociodemographic and clinical characteristics were compared between groups (VIT vs non-VIT) using the Chi-squared test for qualitative variables or with the t-test or the Mann-Whitney test for numerical variables. Agreement between diagnostic methods was evaluated by Bland–Altman analysis and Lin's concordance correlation coefficient. Paired differences between methods were assessed using the Wilcoxon signed-rank test. A p-value < 0.05 was considered statistically significant. All analyses were performed using R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Population Characteristics

A total of 123 patients were included in the study, of whom 32 (26.0%) were receiving ongoing VIT with a mean duration of 6.2 years. Among these, 15 patients (46.9%) were undergoing VIT with *Vespula* venom, 6

(18.8%) with *Apis mellifera*, and 3 (9.4%) with *Vespa crabro*. Dual venom immunotherapy was administered to 7 patients (21.9%) receiving both *Vespula spp.* and *Polistes dominula* venom extracts, and to 1 patient (3.1%) receiving both *Vespula spp.* and *Apis mellifera*. The study population comprised 121 Caucasian patients (98.4%) and 2 Hispanic patients (1.6%). The distribution of systemic reactions according to the Mueller classification was as follows: grade I, 26 patients (21.1%); grade II, 17 (13.8%); grade III, 35 (28.5%); and grade IV, 45 (36.6%). Demographic and clinical characteristics of the study population are summarized in Table 1. Overall, the two subgroups showed largely comparable demographic and clinical characteristics. Patients receiving VIT exhibited a lower prevalence of atopy compared with those not receiving VIT (6.3% vs. 23.1%, $p = 0.037$). No significant differences were observed in age, sex distribution, chronic spontaneous urticaria, mastocytosis, or total IgE levels. Results of skin testing with *Apis mellifera* and *Vespula spp.* venom according to VIT status are summarized in Table 2. Wheal areas obtained with conventional SPT, Soluprick and IDT were broadly comparable between patients receiving and not receiving VIT. Similar patterns were observed for both venoms across all diagnostic methods, with no evidence of clinically relevant differences between the two groups.

Comparative analysis of skin testing methods for *Apis mellifera* venom

Good agreement was observed between Soluprick and SPT for *Apis mellifera*, as indicated by a high concordance correlation coefficient ($CC=0.77$) and limited bias in Bland–Altman analysis, as shown in Figure 1A. In contrast, agreement between Soluprick and IDT (0.1 and 1 $\mu\text{g/mL}$) was poor, with substantial systematic differences and low concordance, suggesting that these methods are not interchangeable (Figure 1B and 1C). In both ID comparisons, a clear trend in the Bland–Altman plots was observed, with increasing differences at higher mean values, indicating the presence of proportional bias. This suggests that the disagreement between methods is not constant across the measurement range, limiting their interchangeability, particularly at higher values. Paired Wilcoxon tests, described in Figure 2, showed no significant difference between Soluprick and SPT 100 $\mu\text{g/mL}$ ($p = 0.29$) for *Apis mellifera*, whereas highly significant differences were observed for IDT (0.1 and 1 $\mu\text{g/mL}$; $p < 0.001$). These findings confirm the presence of systematic differences between Soluprick and IDT measurements, while supporting comparability with SPT. These findings are consistent with the patterns observed in the Bland–Altman analyses and support the lack of interchangeability between Soluprick and IDT.

Comparative analysis of skin testing methods for *Vespula spp.* venom

Regarding *Vespula spp.*, agreement between Soluprick and other skin methods (SPT 100 $\mu\text{g/mL}$, ID 0.1 $\mu\text{g/mL}$ and ID 1 $\mu\text{g/mL}$) was consistently low. Even the comparison with SPT 100 $\mu\text{g/mL}$ showed only weak concordance ($CC=0.31$), while IDT demonstrated very poor agreement ($CC \leq 0.10$). As illustrated in the Bland–Altman analysis in Figure 3, the first comparison showed evidence of heteroscedasticity, with increasing variability of differences at higher mean values. In contrast, the other two comparisons demonstrated a clear systematic bias, with consistent deviations from zero across the measurement range. Comparison of Soluprick and conventional SPT for *Vespula spp.* venom demonstrated a statistically significant difference in paired testing (Wilcoxon signed-rank test, $p = 0.014$), indicating the presence of a modest but non-negligible systematic bias. Highly significant differences were observed for both intradermal methods ($p < 0.001$), confirming substantial disagreement. These findings suggest that, in contrast to other allergens, even SPT 100 $\mu\text{g/mL}$ may not be fully interchangeable with Soluprick in *Vespula spp.* measurements.

Discussion and Conclusions

Skin testing remains a cornerstone of the diagnostic work-up of Hymenoptera venom allergy and is recommended by current European guidelines as an essential component of the evaluation of patients with suspected venom allergy (2,8). While IDT is generally considered the most sensitive diagnostic approach, high-concentration venom SPT is increasingly used in routine clinical practice as a less invasive and more practical alternative. The practical applicability of SPT at 300 µg/mL should also be considered in the context of the heterogeneous availability of 300 µg/mL venom preparations across European countries, which may influence its implementation in routine clinical practice. However, evidence comparing the performance of these methods remains limited. In this context, the present multicentre real-life study evaluated the relationship between Soluprick, SPT, and IDT in patients undergoing diagnostic assessment for Hymenoptera venom allergy. The main finding was that the comparability of Soluprick varied according to the venom tested. For *Apis mellifera* venom extract, Soluprick showed good comparability with conventional SPT performed at 100 µg/mL, whereas concordance with IDT was poor. Royer et al. reported improved SPT results with increasing venom concentrations up to 300 µg/mL compared with conventional concentrations (11). More recently, Möbs et al. evaluated a similar high-concentration SPT approach and compared SPT300 with conventional SPT and IDT, also incorporating venom-specific IgE measurements (12). Their findings supported the potential diagnostic value of SPT 300 µg/mL, while also highlighting its limitations, particularly with bee venom. In our study, high-concentration SPT 300 µg/mL similarly showed poor concordance with IDT, supporting its complementary rather than interchangeable role. While Möbs et al. provided additional information through venom-specific IgE measurements, our multicentre real-life study specifically assessed the agreement between Soluprick and IDT, providing complementary evidence on the practical role and limitations of high-concentration SPT. (3,8,12). Consistent with these observations, our results indicate that high-concentration SPT cannot replace IDT. Another relevant finding was the different pattern of results observed for *Apis mellifera* and *Vespula spp.* venom extracts. While Soluprick and SPT 100 µg/mL showed good comparability for *Apis mellifera* venom extract, agreement was substantially lower for *Vespula spp.*, with significant differences also emerging between the two prick-based methods. Although the reasons for this discrepancy cannot be clarified by the present study, differences in venom composition, extract standardization, and allergenic content among diagnostic preparations may contribute (15). From a clinical perspective, these findings support current European and Italian recommendations, which continue to consider IDT the most sensitive skin test technique (2,3,8). It should also be noted that the use of high-concentration venom extracts for SPT may increase the risk of irritative skin reactions, particularly with honeybee venom, as reported in the S2k Guideline by Ruëff et al. (8). This aspect should be taken into consideration when interpreting positive reactions obtained at the highest SPT concentration. Therefore, a negative Soluprick result should not replace further evaluation with IDT when indicated. Moreover, accurate assessment of venom sensitization remains crucial not only for the initial diagnostic work-up but also for the longitudinal management of patients undergoing VIT (3, 16-19). Notably, both patients undergoing VIT and patients evaluated at diagnosis prior to VIT were included in our study. No significant differences in skin test responses were observed between these groups, suggesting that VIT status did not substantially influence the overall patterns identified in the present analysis. Although the duration of VIT and the timing of skin testing in relation to immunotherapy may influence skin reactivity, the mean duration of VIT in our cohort was 6.2 years. These findings suggest that VIT status did not substantially affect the comparative results between the different skin testing methods. The strengths of this study are its multicentre design and real-world setting. Limitations include its retrospective nature and the lack of systematic sIgE testing to whole venom extracts and/or molecular allergens. The absence of an independent diagnostic reference standard also means that our findings should be interpreted primarily as measures of agreement between skin testing methods rather than diagnostic accuracy.

In conclusion, Soluprick showed good comparability with SPT 100 µg/mL only for *Apis mellifera* venom extract, whereas concordance with IDT was poor for both venoms. These findings indicate that Soluprick cannot be considered a surrogate for IDT in the routine diagnosis of Hymenoptera venom allergy. IDT remains an essential component of the diagnostic evaluation of patients with suspected venom allergy. Prospective studies are warranted to further define the role of high-concentration prick testing within contemporary diagnostic algorithms.

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Conflict of Interests: the authors declare no conflict of interest.

Ethics Statement: The study was conducted in accordance with the ethical principles for medical research involving human subjects (WMA declaration of Helsinki and its later amendments). Informed consent was obtained from all individual participants included in the study.

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Baseline characteristics	Overall population	Valid N	Receiving VIT	Valid N	Not receiving VIT	Valid N	p-value
Sex, n (%)		123		32		91	0.999
- F	48 (39)		12 (37.5)		36 (39.6)		
- M	75 (61)		20 (62.5)		55 (60.4)		
Age (years), mean (SD)	52.9 (16.5)	123	56.7 (15.6)	32	51.5 (16.8)	91	0.117
Comorbidities, n (%)		123		32		91	
- Atopic comorbidities	23 (18.7)		2 (6.3)		21 (23.1)		0.037
- CSU	5 (4.0)		0 (0.0)		5 (5.5)		0.325
- Mastocytosis	5 (4.0)		1 (3.0)		4 (4.4)		0.999
IgE, median (IQR)	138 (53.3-254.5)	123	196.5 (88.7-272.3)	32	123 (47.5-233)	91	0.186

Table I. Baseline demographic and clinical characteristics of the study population according to venom immunotherapy (VIT) status.

Data are presented as n (%), mean $\pm$ SD, or median (IQR), as appropriate. P-values refer to comparisons between patients receiving and not receiving VIT at the time of evaluation. Legend: CSU, chronic spontaneous urticaria.

Variable Median area (IQR)	Overall population (n=123)	Receiving VIT (n=32)	Not receiving VIT (n=91)	p-value
Area <i>Apis m.</i> SPT	0 (0-0)	0 (0-0)	0 (0-0)	0.892
Area <i>Apis m.</i> Soluprick	0 (0-0)	0 (0-8.8)	0 (0-0)	0.202
Area <i>Apis m.</i> ID 0.1	0 (0-42.6)	0 (0-53)	0 (0-0)	0.292
Area <i>Apis m.</i> ID 1	0 (0-0)	0 (0-70.7)	0 (0-0)	0.136
Area <i>Vespula spp.</i> SPT	0 (0-5.5)	0 (0-7.1)	0 (0-4.7)	0.767
Area <i>Vespula spp.</i> Soluprick	3.1 (0-12.6)	0 (0-15.7)	3.1 (0-12.6)	0.888
Area <i>Vespula spp.</i> ID 0.1	49.5 (0-78.5)	40.8 (3.9-70.7)	54.9 (0-84.8)	0.621
Area <i>Vespula spp.</i> ID 1	70.7 (6.9-94.8)	66.8 (39.9-92.3)	75.4 (0-102.1)	0.779

Table II. Comparison of wheal areas obtained with conventional SPT (100 μ g/mL), Soluprick (300 μ g/mL) and intradermal (ID) (0.1 and 1 μ g/mL) testing for *Apis mellifera* and *Vespula spp.* venom according to VIT status.

Data are presented as median wheal area (IQR). P-values refer to comparisons between patients receiving and not receiving VIT at the time of evaluation. SPT, skin prick test; ID, intradermal test.

Figure 1. Bland–Altman plots and concordance analyses (CC) comparing Soluprick with SPT (1A), ID 0.1(1B), and ID 1(1C) for *Apis mellifera*. Bland–Altman plots show the differences versus the mean of the two methods (with horizontal lines representing the mean difference and limits of agreement), while scatterplots display the corresponding concordance (the solid line represents the bisector, corresponding to perfect agreement between methods).

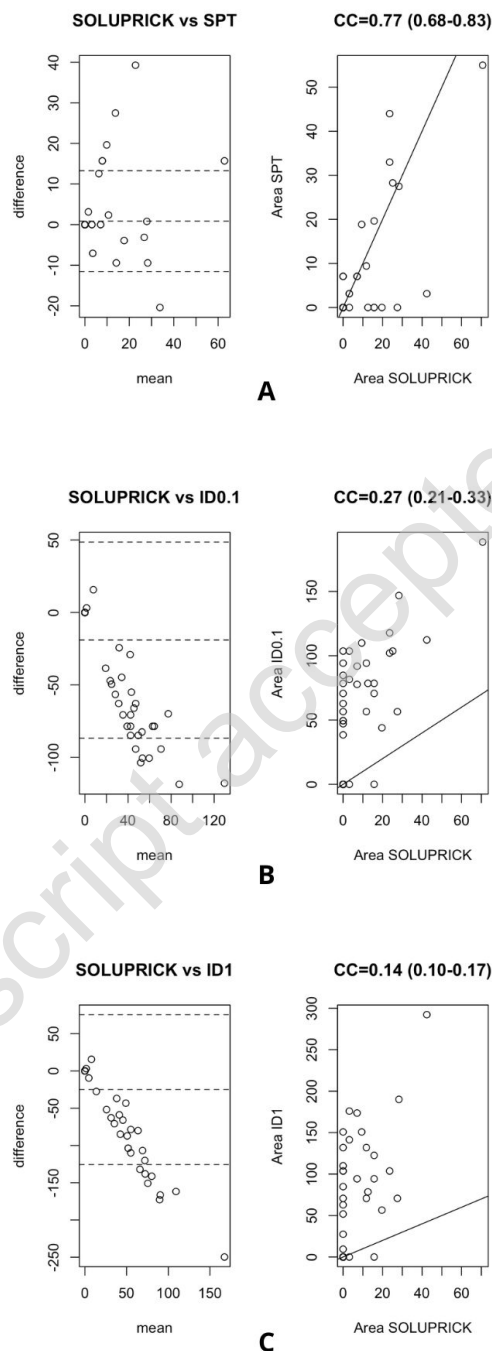


Figure 2. Boxplots of paired differences in area measurements between Soluprick 300 $\mu\text{g/mL}$ and alternative methods (SPT 100 $\mu\text{g/mL}$, ID 0.1 $\mu\text{g/mL}$ and ID 1 $\mu\text{g/mL}$) for *Apis mellifera*.

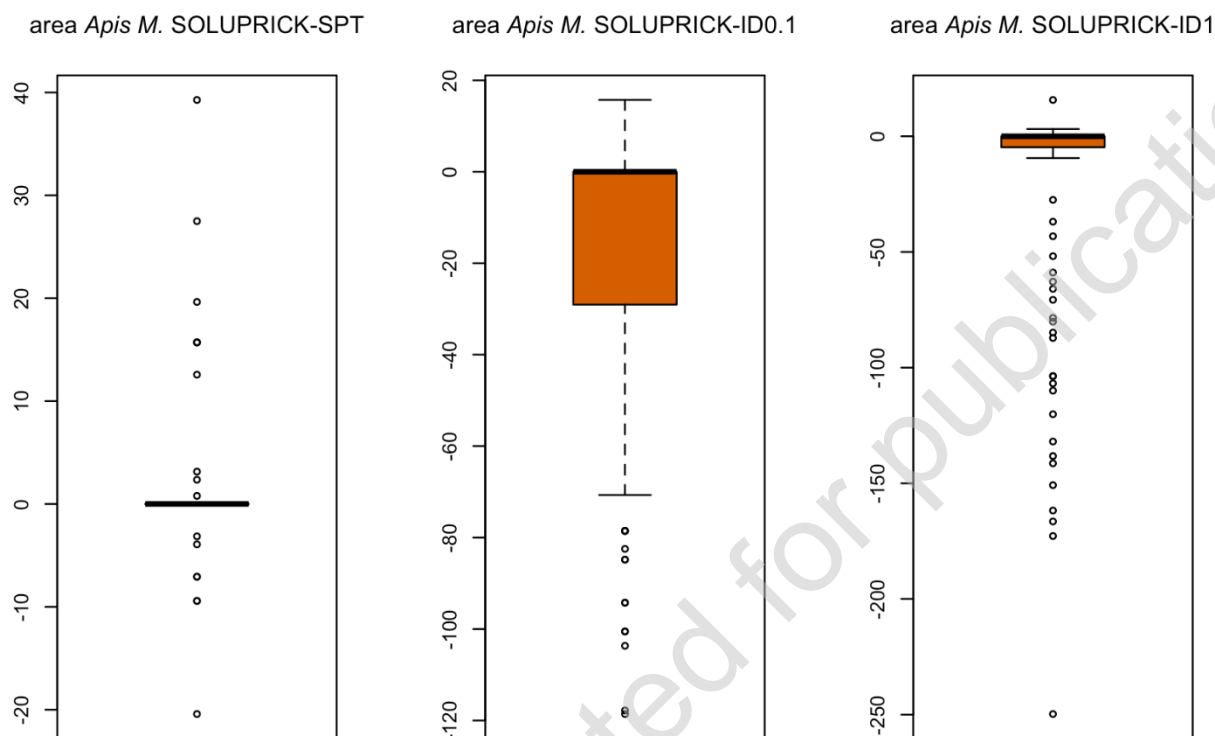


Figure 3. Bland–Altman plots and concordance analyses (CC) comparing Soluprick with SPT (3A), ID 0.1(3B), and ID 1(3C) for *Vespula* spp. Bland–Altman plots show the differences versus the mean of the two methods (with horizontal lines representing the mean difference and limits of agreement), while scatterplots display the corresponding concordance (the solid line represents the bisector, corresponding to perfect agreement between methods).

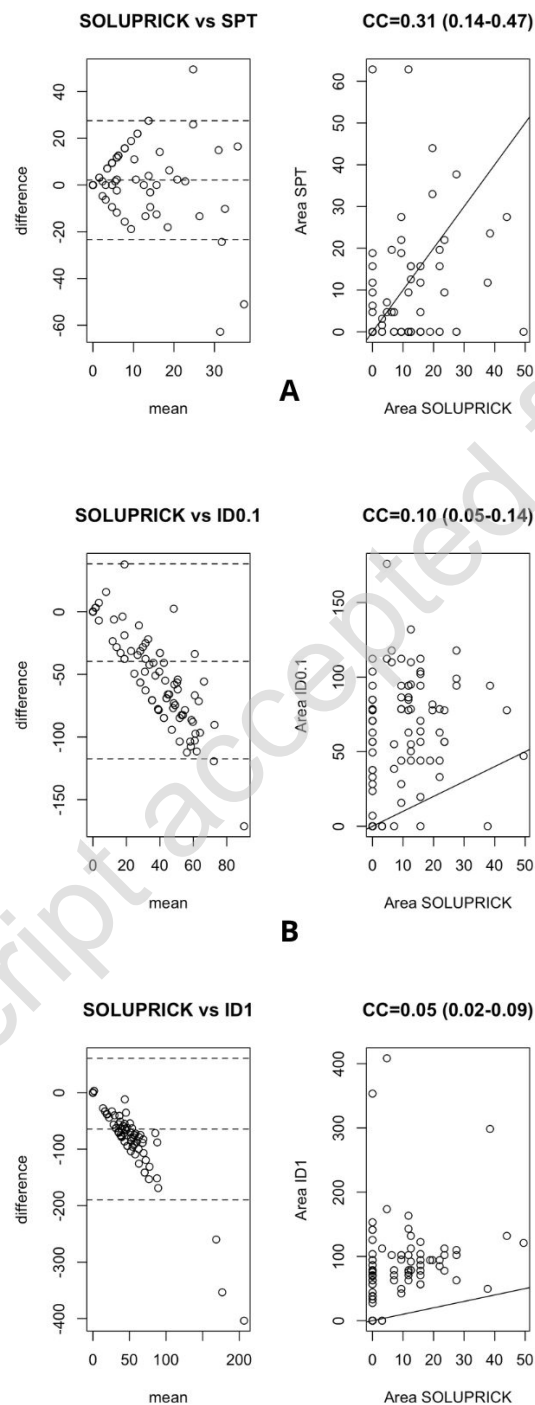


Figure 4. Boxplots of paired differences in area measurements between Soluprick 300 $\mu\text{g/mL}$ and alternative methods (SPT 100 $\mu\text{g/mL}$, ID 0.1 $\mu\text{g/mL}$ and ID 1 $\mu\text{g/mL}$) for *Vespula spp.*

