

Development and Evaluation of an Agro-healing Program for Adults Addressing Burnout Risk Factors

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Abstract. This study evaluated, using a single-group pre-post design, a plant-mediated agro-healing program in nonclinical adults screened for elevated perceived stress [Perceived Stress Scale (PSS-10) score ≥ 17]. A total of 21 participants completed 8 weekly 90-min sessions that combined herb-based olfactory stimulation, farm work-related physical activity, and structured group-based psychological exercises. Self-report measures of depression, anxiety, perceived stress, psychological flexibility, self-esteem, and life satisfaction were administered at baseline and postintervention, and untargeted blood-based metabolomics was used to explore stress-related metabolites. Indicators commonly linked to burnout changed favorably: perceived stress, anxiety, and depression decreased ($P < 0.05$), while psychological flexibility ($P < 0.01$) and life satisfaction ($P < 0.001$) increased. Psychological flexibility showed expected correlations with anxiety, depression, stress, and self-esteem ($P < 0.05$ – 0.01). Metabolomics suggested post-intervention reductions in sphingosine—a stress-linked lipid mediator—alongside complementary shifts across amino-acid and fatty-acid pathways. These findings indicate that a plant-mediated agro-healing program may support stress reduction, enhanced self-regulatory capacity, and plausible physiological modulation in nonclinical adults with high perceived stress. While relevant to burnout-related risk reduction, we refrained from labeling participants as “at risk of burnout” in the absence of diagnostic classification. Metabolomic signals are hypothesis generating and warrant confirmation via targeted assays and adequately powered, preregistered randomized controlled trials with longer follow-up and validated burnout instruments.

Modern society is characterized by high levels of stress, intense competition, and a decline in overall well-being. Although Korea is often portrayed as a leisure-centered society that prioritizes quality of life (Kim and Park 2014), official time-use statistics show only a modest rebound in leisure time—after declining from 2009 to 2014 and remaining essentially flat by 2019 (4 h 47 min; 19.9%

of the day), the 2024 Time Use Survey reports 5 h 8 min (21.4%), with a substantial share accounted for by media use (Statistics Korea 2014, 2019, 2024). These patterns are associated with strained work-life balance and lower physical/mental health and life satisfaction and align with Korea’s below-Organization for Economic Co-operation and Development-average performance on several “better life”

dimensions (Obled et al. 2024). Consistent with this trend, national indicators show lower life satisfaction at older ages across the lifespan (Statistics Research Institute 2024).

Within workplaces, burnout is defined in the 11th revision of the International Classification of Diseases (ICD-11) as the result of chronic workplace stress that has not been successfully managed (World Health Organization 2019). According to the Job Demands-Resources (JD-R) model, a combination of excessive job demands and limited resources triggers a health-impairment pathway that culminates in emotional exhaustion, cynicism, and reduced professional efficacy (Demerouti et al. 2001; Schaufeli and Taris 2014). Empirical evidence from meta-analyses and longitudinal/cross-lagged studies shows that high psychological demands (e.g., time pressure, role conflict) and deficits in resources significantly predict subsequent burnout, whereas job resources buffer these effects (Hakanen et al. 2008; Lesener et al. 2019). At the same time, individual vulnerabilities (e.g., stress sensitivity, low self-esteem), client-related demands (e.g., sustained emotional labor, surface acting, exposure to aggression/trauma, large caseloads), and organizational conditions (e.g., low decision latitude and supervisory support, role conflict/ambiguity, effort-reward imbalance, perceived unfairness/values mismatch, long hours, shift work, understaffing) compound risk—patterns documented across service settings (Aiken et al. 2002; Colquitt et al. 2001; Demerouti et al. 2001; Grandey 2000; Hochschild 1983; Karasek and Theorell 1990; Maslach and Leiter 1997, 2016; Nielsen and Einarsen 2012; Shanafelt et al. 2015; Siegrist 1996).

The salience of burnout increased after COVID-19, with large surveys indicating high self-reported burnout among workers (e.g., 55.1% in a Korean office-worker sample; 52% of US employees in 2023). Importantly, ICD-11 classifies burnout as an occupational phenomenon rather than a medical diagnosis, and national handling varies (e.g., Sweden’s ICD-10-SE F43.8A “Stress-related Exhaustion Disorder” for sick-leave certification; Finland not treating job burnout per se as an illness entitling benefits; the Netherlands managing burnout/overwork within occupational-disease and return-to-work pathways) (GALLUP 2023; Netherlands Centre for Occupational Diseases 2000, 2013; Swedish Parliament 2003; TENK, 2009, 2019; World Health Organization 2019). Conceptually and empirically, these observations converge with the JD-R framework: elevated perceived stress and job demands are robust antecedents of burnout—especially emotional exhaustion—while resources function as buffers (Bakker 2023; Demerouti et al. 2001; Hakanen et al. 2008; Lesener et al. 2019).

Against this backdrop, South Korea enacted the Act on the Research, Development, and Promotion of Healing Agriculture to meet growing public demand for preventive health measures by systematically using agricultural and rural resources for therapeutic purposes (Introduction of Korean Law Information Center 2021). Agro-healing—

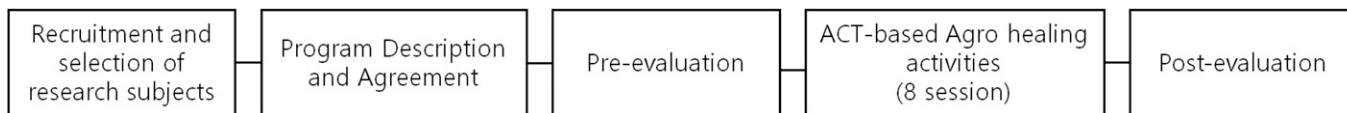


Fig. 1. Experimental protocol. ACT = acceptance and commitment therapy.

also discussed internationally as *green care* or *care farming*—refers to structured, goal-oriented interventions that mobilize farm-based resources (e.g., field-scale crop production, seasonal sowing–harvest cycles, animal husbandry, rural landscapes, farm social settings) under professional facilitation to promote mental and physical well-being. Unlike therapeutic horticulture/horticultural therapy, which are plant-mediated programs often delivered in clinical or community venues and need not involve a farm, healing agriculture embeds participants in a working farm environment, engages them in productive agricultural routines (e.g., planting, weeding, harvesting, livestock care), and leverages multisensory rural contexts and farm social relations (Bragg 2020; Hassink et al. 2020; Iancu et al. 2015; Kim 2016; Park and Kang 2017; Rural Development Administration 2013; Yoo et al. 2021).

According to prior research, agro-healing approaches are associated with reductions in depression, anxiety, and stress and with improvements in self-esteem, self-efficacy, life satisfaction, and physiological indicators (e.g., blood pressure); benefits are also reported in community and older-adult populations and in care-farming initiatives in the United Kingdom and the Netherlands (Bragg 2020; Hassink et al. 2020; Jang et al. 2019; Jeong et al. 2019; Park and Kang 2017). Building on this literature and on evidence that burnout correlates positively with depression/anxiety and negatively with self-esteem/resilience (Hao 2023), that self-esteem mediates stress–burnout links (Liu 2023), and that acceptance influences ego depletion and physiological stress responses (Lee et al. 2021), the present study applied an 8-week, acceptance and commitment therapy (ACT) theory-based, plant-mediated agro-healing program to nonclinical adults with elevated perceived stress, with the aim of preventing burnout. We evaluated pre–post changes in perceived stress, anxiety, depression,

psychological flexibility, self-esteem, and life satisfaction and explored the potential for physiological stress regulation by profiling blood-based metabolites.

Material and Methods

Participants and eligibility. Community-dwelling adults aged 20 to 59 years were recruited via district-office bulletin boards in

Seoul and online communities between Jun and Jul 2023. Inclusion requirements included age 20 to 59 years, ability to perform light physical activity; no self-reported allergy to study plants, and elevated perceived stress defined a priori as a Perceived Stress Scale (PSS-10) score ≥ 17 (moderate or higher). PSS-10 was administered at prestudy screening and reconfirmed at baseline; only individuals with PSS-10 scores ≥ 17 were

Table 1. Session-by-session agro-healing and ACT activities.

| Session | Activity | | Description |
|---------|---|--------------------|---|
| | Agro healing | ACT | |
| 1 | Leveling the ground | Being present | <ul style="list-style-type: none"> • Taking a mindful walk around the care farm • Touching the soil while reflecting on one's present self • Removing grass and debris; leveling the ground for planting • Writing in a mindfulness notebook; short meditation |
| 2 | Planting seedlings | Cognitive defusion | <ul style="list-style-type: none"> • Walking through herb beds • Feeling sensations through herbs • Planting herb seedlings; designing the garden; watering |
| 3 | Pest control | Acceptance | <ul style="list-style-type: none"> • Reflective writing and meditation • Walking and observing the field • Discussion: "What happens if you don't manage pests?" • Weeding, watering, preparing eggshell calcium spray |
| 4 | Planting herb seedlings in pots | Self as context | <ul style="list-style-type: none"> • Reflective writing and meditation • Walking mindfully • Observing self-awareness while touching and smelling herbs • Weeding, watering, decorating pots, transplanting seedlings • Reflective writing and meditation • Write down your emotions and sensations in a mindfulness notebook |
| 5 | Creating an automatic irrigation system | Value | <ul style="list-style-type: none"> • Meditating • Walking and exploring the value of herbs and personal values • Weeding, watering • Constructing a simple automatic irrigation system (Arduino-based) • Harvesting herbs |
| 6 | Herb cuttings | Committed action | <ul style="list-style-type: none"> • Reflective writing and meditation • Mindful walking • Reflecting on commitment to one's values through herbs • Weeding, watering, harvesting • Making egg yolk oil and preparing cuttings |
| 7 | Making herb scent pouches | Committed action | <ul style="list-style-type: none"> • Reflective writing and meditation • Walking and reaffirming commitment to personal values • Pulling weeds, watering, harvesting herbs • Making egg yolk oil; creating herbal scent pouches |
| 8 | Making herb plaster air freshener | Committed action | <ul style="list-style-type: none"> • Reflective writing and meditation • Mindful walking; reaffirming values • Weeding, watering, harvesting herbs • Making plaster herb air fresheners • Reflective writing and meditation |

ACT = acceptance and commitment therapy.

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Table 2. Comparison of changes in depression (PHQ-9), stress (PSS), life satisfaction (SWLS), and self-esteem scores.

| Variables | Pre-test (mean ± SD) | Post-test (mean ± SD) | t | P |
|-------------|----------------------|-----------------------|--------|---------------------|
| PHQ-9 | 7.09 ± 5.17 | 4.29 ± 3.16 | 2.248 | 0.036 ⁱ |
| PSS | 28.24 ± 4.48 | 25.10 ± 4.85 | 2.745 | 0.012 ⁱ |
| Self-esteem | 28.76 ± 4.47 | 30.24 ± 4.32 | -3.100 | 0.006 ⁱⁱ |
| SWLS | 21.38 ± 5.29 | 23.24 ± 4.81 | -2.434 | 0.024 ⁱ |

ⁱ Significant at $P < 0.05$ using Paired t test.

ⁱⁱ Significant at $P < 0.01$ using Paired t test.

PHQ-9 = Patient Health Questionnaire 9; PSS = Perceived Stress Scale; SD = standard deviation; SWLS = Satisfaction with Life Scale.

Table 3. Comparison of changes in anxiety (BAI) and psychological flexibility (AAQ-II).

| Variables | Pre-test (mean ± SD) | Post-test (mean ± SD) | Z | P |
|-----------|----------------------|-----------------------|---------------------|----------------------|
| BAI | 11.33 ± 10.33 | 6.81 ± 5.62 | -2.078 ⁱ | 0.038 ⁱⁱⁱ |
| AAQ-II | 26.33 ± 7.81 | 23.05 ± 5.96 | -2.751 ⁱ | 0.006 ⁱⁱⁱ |

ⁱ Positive rank criteria.

ⁱⁱ Significant at $P < 0.05$ using Wilcoxon signed rank test.

ⁱⁱⁱ Significant at $P < 0.01$ using Wilcoxon signed rank test.

AAQ-II = Acceptance and Action Questionnaire, version 2; BAI = Beck Anxiety Inventory.

enrolled. Exclusion criteria included current psychiatric diagnosis, ongoing psychotherapy or psychotropic medication initiation/change within 3 months, and acute medical conditions. No validated burnout instrument was used for eligibility; the sample was nonclinical and enriched for elevated perceived stress. Screening occurred before enrollment. The study protocol was approved by the Institutional Review Board of Konkuk University (Approval 7001355-202310-HR-709), and all participants provided written informed consent. Adverse events were monitored each session; no serious adverse events were reported. Participants received a \$15 stipend upon study completion.

Study design and setting. We conducted a single-group pre-post study at an urban agricultural experience center in Seoul, South Korea, using vegetable gardens, walking paths, and outdoor lecture areas. During the intervention period, the mean ambient temperature was 27.25 ± 2.71 °C, and the relative humidity was $71.35 \pm 8.98\%$ (Fig. 1).

Intervention. The intervention was systematically developed using the Intervention Mapping framework. A preliminary needs assessment was conducted to refine session themes and target psychosocial needs. Based on these findings, we structured an ACT-integrated agro-healing program in which each participant was assigned a 3-m × 1-m garden plot and engaged in seed sowing, seedling transplanting, watering, weeding, and pest management.

Herbs (peppermint, lemon balm, spearmint, lavender, rosemary) were selected with reference to prior reports of stress-, anxiety-, and mood-related benefits.

To enhance psychological benefits, the principles of ACT were embedded across all sessions. Gardening activities were mapped onto the six core ACT processes—present-moment awareness, cognitive defusion, acceptance, self-as-context, values clarification, and committed action—drawing on established stress- and mood-focused protocols (Bond and Bunce 2000; Bond and Hayes 2002; Block 2002; Zettle and Raines 1989).

Session structure and facilitation. The intervention comprised 8 weekly sessions (90 min each) centered on hands-on horticultural and farm-based activities designed to promote relaxation, sensory engagement, and restorative experiences in nature. Sessions were led by one horticultural therapist (lead facilitator) and supported by two assistant facilitators (research staff) who provided technical guidance and emotional support throughout the activities. Each session concluded with a brief 3- to 10-min relaxation or mindfulness practice (e.g., breath awareness, body scan) to support calmness and present-moment awareness. A session-by-session outline is provided (Table 1).

Measures. Psychological outcomes were assessed preintervention (Week 0) and post-intervention (Week 8) using validated self-report instruments: Beck Anxiety Inventory

Table 4. Results of correlation analysis between variables.

| Variables | BAI | PHQ-9 | PSS | Self-esteem | AAQ-II | SWLS |
|-------------|---------------------|---------------------|----------------------|---------------------|--------|------|
| BAI | 1 | | | | | |
| PHQ-9 | 0.400 | 1 | | | | |
| PSS | 0.221 | 0.330 | 1 | | | |
| Self-esteem | -0.208 | -0.135 | -0.516 ⁱⁱ | 1 | | |
| AAQ-II | 0.699 ⁱⁱ | 0.566 ⁱⁱ | 0.513 ⁱ | -0.488 ⁱ | 1 | |
| SWLS | -0.321 | -0.347 | -0.495 ⁱ | 0.690 ⁱⁱ | -0.416 | 1 |

ⁱ Significant at $P < 0.05$ using Pearson's correlation analysis.

ⁱⁱ Significant at $P < 0.01$ using Pearson's correlation analysis.

AAQ-II = Acceptance and Action Questionnaire, version 2; BAI = Beck Anxiety Inventory; PHQ-9 = Patient Health Questionnaire 9; PSS = Perceived Stress Scale; SWLS = Satisfaction with Life Scale.

(BAI) (Yuk and Kim 1997), Patient Health Questionnaire 9 (PHQ-9) (Ahn et al. 2013), PSS-10 (Park and Seo 2010), Acceptance and Action Questionnaire, version 2 (AAQ-II) for psychological (in)flexibility (Heo et al. 2009), the Rosenberg Self-Esteem Scale (Rosenberg 1979), and the Satisfaction with Life Scale (SWLS) (Ryu 1996). A brief postprogram satisfaction survey (quantitative items plus open-ended feedback) captured perceived benefits and suggested improvements. Internal consistency coefficients for this sample are reported under "Results."

Metabolomic analysis. Blood and saliva samples were used for metabolite evaluation. Trained professionals collected blood samples (5 mL) before and after the experiments. They were placed in ice packs and transported to the analysis site. The samples were maintained at room temperature for 20 min and separated by centrifugation at 1000 g_n for 10 min at 4 °C. Serum aliquots were stored at -70 °C. A 100- μ L aliquot of serum was mixed with 600 μ L of cold methanol containing the internal standard (2-chlorophenylalanine, 10 mg/L), vortexed for 1 min, homogenized for 10 min at 30 Hz using a mixer mill (MM400; Retsch, Haan, Germany), and sonicated for 10 min. The suspension was stored at -20 °C for 60 min before centrifugation at 13,000 g_n at 4 °C for 10 min. The supernatant was filtered through a 0.2- μ m polytetrafluoroethylene (PTFE) filter to obtain the metabolite extract. For ultra-high performance liquid chromatography (UHPLC)-Orbitrap-tandem mass spectrometry (MS/MS) analysis, the extract was diluted 2-fold with methanol and filtered using a 0.2- μ m PTFE filter. For gas chromatography-time-of-flight-mass spectrometry (GC-TOF-MS) analysis, a 100- μ L aliquot of the extract was completely dried using a speed vacuum for further derivatization.

Human saliva samples (3 mL) were collected in a 50-mL Falcon tube, as described by Choi et al. (2014), with slight modifications. After collection, the samples were placed in ice packs and transported to the analysis site. The samples were centrifuged at 10,000 g_n at 4 °C for 10 min, and the supernatants were stored at -70 °C. A 500- μ L aliquot of saliva was mixed with 1 mL of acetonitrile containing the internal standard (2-chlorophenylalanine, 10 mg/L), vortexed for 10 s, and centrifuged at 13,000 g_n at 4 °C for 10 min. The supernatant was filtered through a 0.2- μ m PTFE filter and concentrated using a speed vacuum. The concentrated samples were dissolved in 10% MeOH to achieve a final concentration of 5,000 mg/L and filtered through a 0.2- μ m PTFE filter for UHPLC-Orbitrap-MS/MS analysis.

Data processing and statistical analysis. Pre- and postprogram psychological evaluation items and metabolites were collected and analyzed using SPSS (version 28; IBM Corp., Armonk, NY, USA), with significance set at $P < 0.05$. Metabolomic analysis was conducted using UHPLC-Orbitrap-MS/MS and GC-TOF-MS. UHPLC-Orbitrap-MS/MS analysis of serum and saliva samples and the derivatization method and instrumental conditions

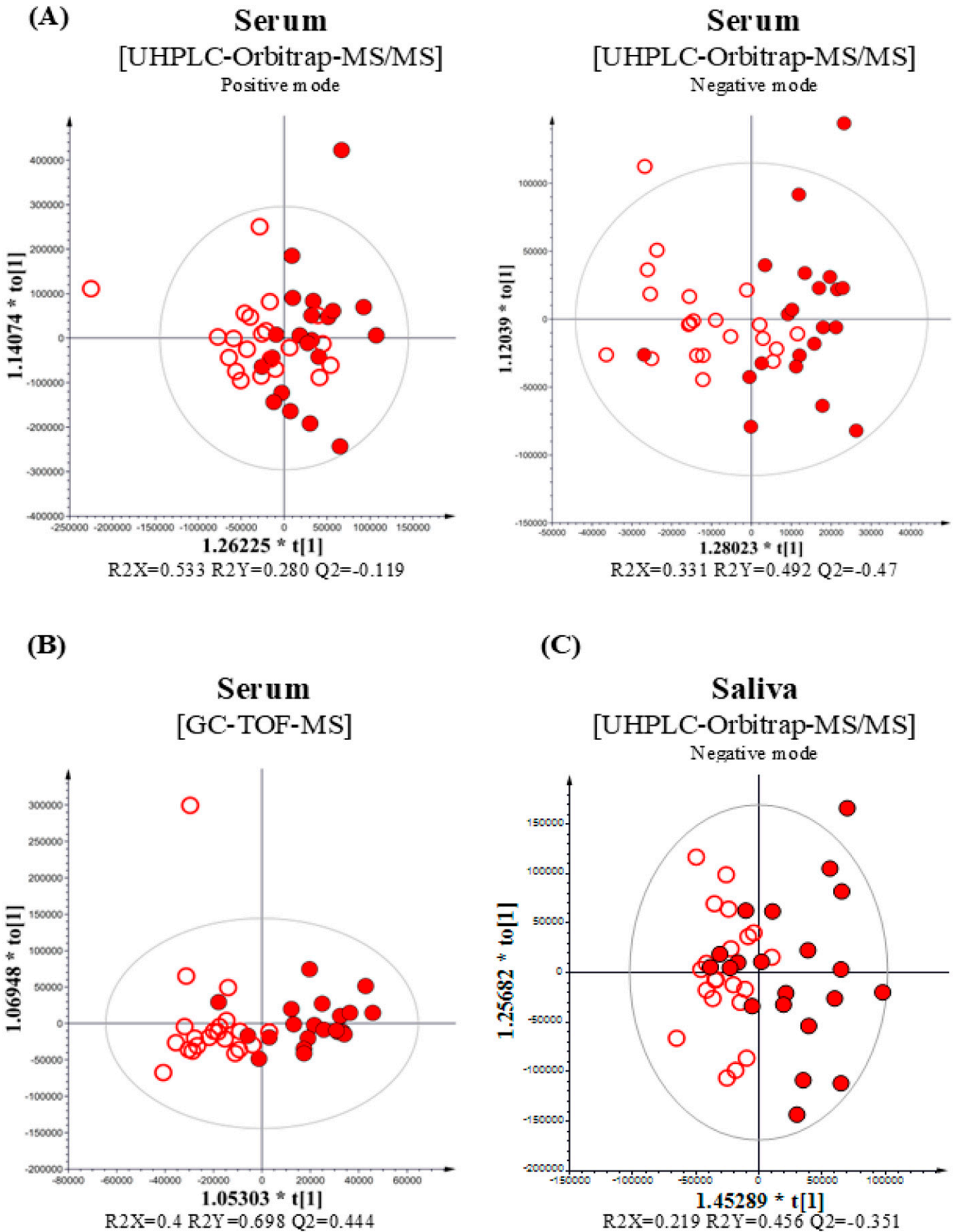


Fig. 2. Orthogonal partial least squares-discriminant analysis (OPLS-DA) score plots. (A, B) Serum samples. (C) Saliva samples. Multivariate analyses were conducted using data sets derived from ultra-high performance liquid chromatography (UHPLC)–Orbitrap–tandem mass spectrometry (MS/MS) (A, C) and gas chromatography–time-of-flight–mass spectrometry (GC-TOF-MS) (B). Open red circles show the pre group, and filled red circles show the post group.

Table 5. Significantly different metabolites in serum identified by UHPLC-Orbitrap-MS/MS between pre and post groups.

| No. | Tentative identification ¹ | VIP | Retention time (min) | Precursor ion (m/z) | MS fragments (m/z) ⁱⁱ | Adduct | Exact mass | Formula | Error(ppm) | ID |
|----------------------------------|--|-------|----------------------|---------------------|----------------------------------|-----------------------|------------|---|------------|-------------------------|
| Amino acids and derivatives | | | | | | | | | | |
| 1 | Leucine | 2.26 | 1.12 | 132.102 | (+) 86.096, 87.100, 69.070 | [M + H] ⁺ | 131.094 | C ₆ H ₁₃ NO ₂ | -3.17 | Lib ⁱⁱⁱ |
| 2 | Phenylalanine | 1.05 | 1.12 | 166.086 | (+) 120.081, 131.049, 121.084 | [M + H] ⁺ | 165.078 | C ₉ H ₁₁ NO ₂ | -3.29 | Lib, MoNA ^{iv} |
| Carboxylic acids and derivatives | | | | | | | | | | |
| 3 | Citric acid | 1.51 | 1.11 | 191.020 | (-) 111.009, 87.009, 85.030 | [M - H] ⁻ | 192.027 | C ₆ H ₈ O ₇ | 0.42 | MoNA |
| 4 | Succinic acid | 3.90 | 1.12 | 117.019 | (-) 73.030, 116.929, 99.009 | [M - H] ⁻ | 118.027 | C ₄ H ₆ O ₄ | 0.99 | Lib, MoNA |
| 5 | Ethyl acetate | 2.60 | 1.23 | 131.070 | (+) 130.159, 59.049, 87.044 | [M + H] ⁺ | 130.063 | C ₆ H ₁₀ O ₃ | -2.82 | Lib |
| Fatty acids and derivatives | | | | | | | | | | |
| 6 | 7-Keto-8-aminopelargonic acid | 4.50 | 5.92 | 188.127 | (+) 170.117, 125.096, 142.122 | [M + H] ⁺ | 187.120 | C ₉ H ₁₇ O ₃ N | -4.26 | MS ^v |
| 7 | Suberic acid | 2.86 | 6.23 | 173.082 | (-) 111.082, 129.092, 172.831 | [M - H] ⁻ | 174.089 | C ₈ H ₁₄ O ₄ | -0.4 | MoNA |
| 8 | Azelaic acid | 4.83 | 6.93 | 187.097 | (-) 125.097, 143.108, 186.114 | [M - H] ⁻ | 188.105 | C ₉ H ₁₆ O ₄ | -0.75 | MoNA |
| 9 | Sebacic acid | 1.96 | 7.51 | 201.113 | (-) 139.113, 157.123, 183.103 | [M - H] ⁻ | 202.120 | C ₁₀ H ₁₈ O ₄ | -0.21 | MoNA |
| 10 | Undecanedioic acid | 1.58 | 8.03 | 215.129 | (-) 197.118, 153.129, 216.133 | [M - H] ⁻ | 216.136 | C ₁₁ H ₂₀ O ₄ | -0.74 | MoNA |
| 11 | Linolenic acid | 1.11 | 10.74 | 279.231 | (+) 261.221, 95.085, 57.070 | [M + H] ⁺ | 278.224 | C ₁₈ H ₃₀ O ₂ | -1.58 | MoNA |
| 12 | 2-Hydroxybutyrate | 3.03 | 1.12 | 103.040 | (-) 57.035, 59.014, 104.043 | [M - H] ⁻ | 104.047 | C ₄ H ₈ O ₃ | 0.91 | MoNA |
| 13 | 3-Carboxy-4-methyl-5-propyl-2-furanpropionate (CMPF) | 4.70 | 8.43 | 239.092 | (-) 195.102, 151.113, 196.106 | [M - H] ⁻ | 240.099 | C ₁₂ H ₁₆ O ₅ | -1.01 | MoNA |
| 14 | Methyl butyrate | 2.49 | 8.72 | 205.143 | (+) 87.044, 194.622, 122.546 | [2M + H] ⁺ | 102.068 | C ₅ H ₁₀ O ₂ | -2.77 | Lib |
| Lipids and derivatives | | | | | | | | | | |
| 15 | Phenyldiethanolamine | 1.08 | 6.39 | 182.117 | (+) 137.098, 165.091, 95.085 | [M + H] ⁺ | 181.110 | C ₁₀ H ₁₅ NO ₂ | -3.28 | MS |
| 16 | Linoleamide | 11.55 | 10.45 | 280.263 | (+) 263.236, 245.226, 95.085 | [M + H] ⁺ | 279.255 | C ₁₈ H ₃₃ NO | -3.71 | MS |
| 17 | Palmitoleylethanolamide | 2.11 | 10.45 | 595.540 | (+) 263.236, 280.263, 245.226 | [2M + H] ⁺ | 297.266 | C ₁₈ H ₃₅ O ₂ N | -2.46 | MS |
| 18 | Sphingosine (C17) | 6.26 | 9.05 | 286.273 | (+) 268.263, 269.266, 100.076 | [M + H] ⁺ | 285.266 | C ₁₇ H ₃₅ NO ₂ | -2.8 | MoNA |
| 19 | Sphingosine | 1.54 | 9.41 | 300.289 | (+) 282.279, 83.085, 97.101 | [M + H] ⁺ | 299.282 | C ₁₈ H ₃₇ NO ₂ | -2.96 | MS |
| 20 | LPC 16:0 | 1.05 | 10.79 | 496.339 | (+) 184.073, 104.107, 86.096 | [M + H] ⁺ | 495.331 | C ₂₄ H ₅₀ NO ₇ P | -3.29 | Lib, MoNA |
| 21 | LPC 18:1 | 2.29 | 11.07 | 522.354 | (+) 184.073, 104.107, 86.096 | [M + H] ⁺ | 521.347 | C ₂₆ H ₅₂ NO ₇ P | -2.7 | MoNA |
| 22 | LPC 18:2 | 1.49 | 10.27 | 520.339 | (+) 184.073, 104.107, 86.096 | [M + H] ⁺ | 519.331 | C ₂₆ H ₅₀ NO ₇ P | -2.67 | MoNA |
| 23 | LPE 18:0 | 1.59 | 11.82 | 480.309 | (-) 283.264, 196.038, 284.267 | [M - H] ⁻ | 481.317 | C ₂₃ H ₄₈ NO ₇ P | -0.49 | MoNA |
| 24 | LPE 18:2 | 3.87 | 10.38 | 476.277 | (-) 279.233, 196.038, 280.236 | [M - H] ⁻ | 477.284 | C ₂₃ H ₄₄ NO ₇ P | -0.65 | MoNA |
| 25 | LPE 20:4 | 1.71 | 10.40 | 500.277 | (-) 303.233, 196.038, 259.243 | [M - H] ⁻ | 501.284 | C ₂₅ H ₄₄ NO ₇ P | -0.62 | MoNA |
| 26 | LPE 18:1 | 2.38 | 11.02 | 478.294 | (-) 281.248, 282.252, 196.038 | [M - H] ⁻ | 479.301 | C ₂₃ H ₄₆ NO ₇ P | -1.02 | MoNA |
| Other | | | | | | | | | | |
| 27 | Camitine | 1.30 | 0.77 | 162.112 | (+) 103.089, 60.081, 163.115 | [M + H] ⁺ | 161.105 | C ₇ H ₁₅ NO ₃ | -3.75 | Lib |
| 28 | Uric acid | 3.53 | 0.82 | 167.021 | (-) 124.015, 168.025, 96.020 | [M - H] ⁻ | 168.028 | C ₅ H ₄ N ₄ O ₃ | -0.31 | MoNA, Lib |
| 29 | Indoxyl sulfate | 1.36 | 5.22 | 212.002 | (-) 79.957, 80.965, 132.046 | [M - H] ⁻ | 213.009 | C ₈ H ₇ NO ₄ S | -0.28 | MoNA |
| 30 | Valeric acid | 1.60 | 11.18 | 235.169 | (+) 179.106, 133.065, 57.070 | [M + H] ⁺ | 234.161 | C ₁₅ H ₂₂ O ₂ | -2.62 | MS |
| Not identified | | | | | | | | | | |
| | N.I. 1 | 1.10 | 1.17 | 142.086 | (+) 125.059, 114.091, 96.081 | | | | | |
| | N.I. 2 | 5.23 | 5.92 | 170.117 | (+) 125.096, 97.101, 107.085 | | | | | |
| | N.I. 3 | 3.62 | 5.92 | 210.109 | (+) 211.113, 165.091, 103.869 | | | | | |
| | N.I. 4 | 1.14 | 6.07 | 244.154 | (+) 245.138, 227.127, 163.111 | | | | | |
| | N.I. 5 | 1.25 | 6.61 | 242.138 | (+) 161.096, 179.107, 189.091 | | | | | |
| | N.I. 6 | 2.05 | 6.62 | 184.133 | (+) 121.101, 139.111, 156.138 | | | | | |
| | N.I. 7 | 1.97 | 6.62 | 202.143 | (+) 184.133, 170.117, 121.101 | | | | | |
| | N.I. 8 | 1.09 | 6.97 | 196.133 | (+) 133.101, 109.101, 151.111 | | | | | |
| | N.I. 9 | 1.74 | 7.17 | 198.148 | (+) 135.117, 152.143, 153.127 | | | | | |
| | N.I. 10 | 1.68 | 7.17 | 216.159 | (+) 198.148, 153.127, 180.138 | | | | | |
| | N.I. 11 | 1.28 | 9.17 | 623.498 | (+) 277.216, 295.226, 179.143 | | | | | |
| | N.I. 12 | 1.24 | 9.54 | 631.561 | (+) 298.273, 263.236, 280.263 | | | | | |

(Continued on next page)

Table 5. (Continued)

| No. | Tentative identification ⁱ | VIP | Retention time (min) | Precursor ion (<i>m/z</i>) | MS fragments (<i>m/z</i>) ⁱⁱ | Adduct | Exact mass | Formula | Error(ppm) | ID |
|---------|---------------------------------------|------|----------------------|------------------------------|---|--------|------------|---------|------------|----|
| N.I. 13 | | 1.14 | 10.01 | 619.467 | (+) 293.210, 275.200, 247.205 | | | | | |
| N.I. 14 | | 1.54 | 10.82 | 627.529 | (+) 157.133, 171.1479, 279.231 | | | | | |
| N.I. 15 | | 2.17 | 11.20 | 249.184 | (+) 193.122, 250.188, 57.070 | | | | | |

ⁱ Identified compounds based on the VIP value (> 1.0) from the OPLS-DA model in Figure 1.

ⁱⁱ Mass fragment patterns detected in negative or positive ion mode.

ⁱⁱⁱ Mass spectrum compared with in-house libraries.

^{iv} Spectra matched to MassBank of North America.

^v Mass spectrum compared with PubChem and HMDB database.

MS = mass spectrometry; MS/MS = tandem mass spectrometry; N.I. = not identified; OPLS-DA = orthogonal partial least squares-discriminant analysis; UHPLC = ultra-high performance liquid chromatography; VIP = variable importance in the projection.

for the GC-TOF-MS analysis of serum samples were performed under identical conditions, as described by Jun et al. (2024). Raw liquid chromatography–mass spectrometry (LC-MS) data files were converted to the mzXML format using ProteoWizard (version 3.0). For serum data sets, the mzXML files were converted to ABF format using the ABF converter for MS-DIAL software (version 5.3) for retention time correction, feature detection, and alignment. For the saliva data sets, mzXML files were uploaded to the XCMS online software (version 3.7.1) to perform retention time correction, peak detection, and alignment. Ion features from both serum and saliva UHPLC-Orbitrap-MS/MS data sets with a relative standard deviation (RSD) of <20% in the quality control (QC) samples were selected for further multivariate analyses. The raw data obtained from GC-TOF-MS were converted to the mzXML format using LECO Chroma TOF software (version 4.44; LECO Corp., St. Joseph, MI, USA). The mzXML files were uploaded to XCMS online software to perform peak selection, retention time correction, and peak alignment. Ion features from serum GC-TOF-MS data sets with a RSD of <30% in the QC samples were selected for further multivariate analyses.

The alignment data were exported to Microsoft Excel. Multivariate statistical analyses were performed using the SIMCA-P+ software (version 12.0), using the pareto scaling method. Orthogonal partial least squares-discriminant analysis (OPLS-DA) was performed to compare differential metabolites between the pre and post groups. Differential metabolites were selected based on their variable importance in the projection (VIP) value of the OPLS-DA model. Potential biomarkers of agro-healing activity were selected by conducting a receiver operating characteristic (ROC) curve analysis, and the area under the ROC curve (AUC) was used to identify and confirm significantly altered metabolites. Pathway analysis was conducted to identify altered metabolic pathways between the pre and post groups. ROC curves and pathway analyses were performed using MetaboAnalyst software (version 6.0). The data sets underwent log transformation and autoscaling.

Statistical analysis. Analyses were performed in SPSS (version 28; IBM Corp.). Normality was evaluated with Shapiro–Wilk tests. For normally distributed variables, paired *t* tests assessed pre–post change; otherwise, the Wilcoxon signed-rank test was used. Pearson correlations summarized associations among outcomes (two-tailed $\alpha = 0.05$). Where applicable, we report effect sizes and note any multiple-comparison adjustments. Missing data were handled by complete-case analysis; session attendance was recorded to characterize adherence.

Results

General characteristics of the subjects. A total of 21 adults (4 men and 17 women) residing in Seoul and Gyeonggi participated in

the study, with a mean age of 41.29 years (SD = 11.59). Nineteen individuals were employed, one was seeking employment, and one was a student.

Pre- and postintervention changes within the group. Normality was assessed with the Shapiro–Wilk test. Variables meeting normality (PHQ-9, PSS, SWLS, and self-esteem) were analyzed with paired *t* tests, showing significant improvements: depression decreased ($t = 2.25$, $P = 0.036$), perceived stress decreased ($t = 2.75$, $P = 0.012$), life satisfaction increased ($t = -2.43$, $P = 0.024$), and self-esteem increased ($t = -3.10$, $P = 0.006$) (Table 2).

Variables not meeting normality (BAI, AAQ-II) were analyzed with the Wilcoxon signed-rank test, revealing lower anxiety (BAI: $Z = -2.08$, $P = 0.038$) and lower psychological inflexibility (AAQ-II: $Z = -2.75$, $P = 0.006$) (Table 3). Note: Higher AAQ-II scores reflect greater inflexibility; thus, a decrease indicates improved psychological flexibility.

Correlations among outcomes. Pearson correlations are summarized in Table 4. AAQ-II correlated positively with BAI ($r = 0.70$), PHQ-9 ($r = 0.57$), and PSS ($r = 0.51$) and negatively with self-esteem ($r = -0.49$). SWLS correlated positively with self-esteem ($r = 0.69$) and negatively with PSS ($r = -0.50$). BAI correlated positively with PHQ-9 ($r = 0.40$). Other pairwise associations were not significant after multiple-comparison correction.

The satisfaction survey results revealed that the participants found value in their knowledge of herbs and reported a sense of stability. However, many felt that the 8-session program was too short and expressed a desire to extend it to 12 sessions and participate in it regularly. Additionally, participants noted that individual gardening activities were often done alone but appreciated that this program was systematically led by an instructor and valued the opportunity to engage in discussions with fellow participants.

Untargeted metabolite profiling in response to agro-healing activity. Metabolite profiling of serum samples was conducted using UHPLC-Orbitrap-MS/MS and GC-TOF-MS to analyze metabolic changes induced by agro-healing activities. The differences between the pre and post groups in serum were visualized in the OPLS-DA plot, which showed distinct separation in both the positive and negative ion modes of the UHPLC-Orbitrap-MS/MS (Fig. 2A), indicating that the overall serum metabolic profile shifted after the intervention. Similar group separation was also observed in the GC-TOF-MS analysis (Fig. 2B), suggesting a consistent change in serum metabolites across analytical platforms.

Metabolites with VIP > 1.0 from the OPLS-DA plots of serum were selected for tentative identification. Based on the LC-MS results, 30 differential metabolites were identified, including 2 amino acids and their derivatives, 3 carboxylic acids and their derivatives, 9 fatty acids and their derivatives, 12 lipids and their derivatives, 4 other metabolites, and 15 unidentified metabolites (Table 5). Based on the GC-MS results, 20 differential metabolites

Table 6. Significantly different metabolites in serum identified by GC-TOF-MS between pre and post groups.

| No. | Tentative identification ⁱ | VIP | Retention time (min) | Unique mass (<i>m/z</i>) | MS fragments (<i>m/z</i>) | ID | TMS |
|----------------------------------|---------------------------------------|------|----------------------|----------------------------|---------------------------------------|-------------------|-----|
| Amino acids and derivatives | | | | | | | |
| 1 | Glycine | 1.68 | 7.74 | 144 | 174 86 175 248 100 59 75 176 133 74 | STD ⁱⁱ | 3 |
| Carboxylic acids and derivatives | | | | | | | |
| 2 | Lactic acid | 4.02 | 5.18 | 117 | 117 191 148 66 190 75 74 118 59 133 | MS ⁱⁱⁱ | 2 |
| 3 | Glycolic acid | 2.84 | 5.18 | 66 | 66 148 177 205 75 69 74 133 149 57 | MS | 2 |
| Fatty acids and derivatives | | | | | | | |
| 4 | 3-Hydroxybutyric acid | 3.39 | 6.25 | 117 | 117 75 191 148 88 174 233 59 130 74 | STD | 2 |
| 5 | 2-Hydroxybutyric acid | 1.43 | 5.81 | 131 | 131 75 148 132 66 74 133 205 59 81 | MS | 2 |
| 6 | Hexadecanoic acid | 2.17 | 13.29 | 117 | 117 75 132 313 129 145 55 131 57 69 | MS | 1 |
| 7 | Elaidic acid | 2.84 | 14.45 | 75 | 75 117 55 129 145 339 69 96 67 81 | MS | 1 |
| 8 | Octadecanoic acid | 1.75 | 14.47 | 117 | 117 75 132 129 145 341 55 57 131 69 | MS | 1 |
| Carbohydrates and derivatives | | | | | | | |
| 9 | Glycerol | 1.95 | 7.41 | 205 | 205 117 103 133 218 148 206 75 74 | MS | 3 |
| 10 | Lyxose | 1.11 | 10.90 | 103 | 103 217 307 75 205 117 74 189 133 89 | MS | 4 |
| 11 | Glucose | 4.61 | 12.51 | 205 | 205 319 160 103 217 117 320 74 206 | STD | |
| 12 | Fructose | 2.98 | 12.52 | 103 | 103 217 307 75 74 133 89 104 117 308 | STD | 5 |
| Lipids and derivatives | | | | | | | |
| 13 | Glyceryl monostearate | 1.03 | 17.28 | 129 | 129 218 103 57 75 55 203 131 191 71 | MS | 2 |
| 14 | Dodecanamide | 2.11 | 14.22 | 59 | 59 72 55 57 60 86 128 114 69 83 | MS | |
| 15 | 1-Monopalmitin | 2.24 | 16.34 | 371 | 371 57 129 55 75 71 239 372 103 203 | MS | 2 |
| 16 | 2-Monopalmitin | 1.98 | 16.35 | 129 | 129 218 103 75 57 55 203 131 71 191 | MS | 2 |
| Other | | | | | | | |
| 17 | <i>O</i> -Ethylhydroxylamine | 1.64 | 4.52 | 146 | 146 119 133 86 205 59 148 130 100 149 | MS | 2 |
| 18 | Hydroxylamine | 1.59 | 8.35 | 119 | 119 133 130 253 178 146 74 100 59 162 | MS | 3 |
| 19 | Boric acid | 2.91 | 4.31 | 221 | 221 263 222 223 133 175 205 264 189 | MS | 3 |
| 20 | Xanthenecarboxylic acid | 2.23 | 6.00 | 181 | 181 152 74 106 75 59 132 91 119 60 | MS | 1 |

ⁱ Identified compounds based on the VIP value (>1.0) from the OPLS-DA model in Figure 1C.

ⁱⁱ Mass spectrum consistent with that of the standard compounds.

ⁱⁱⁱ Mass spectrum compared with the National Institute of Standards and Technology database.

GC = gas chromatography; MS = mass spectrometry; OPLS-DA = orthogonal partial least squares-discriminant analysis; STD = standard; TMS = trimethylsilyl; TOF = time-of-flight; VIP = variable importance in the projection.

were identified, including 1 amino acid and its derivative, 2 carboxylic acids and their derivatives, 5 fatty acids and their derivatives, 4 carbohydrates and their derivatives, 4 lipids and their derivatives, and 4 other metabolites (Table 6). Thus, the metabolic changes associated with agro-healing involved multiple classes of metabolites related to energy production, lipid metabolism, and amino acid/carbohydrate turnover rather than being restricted to a single pathway.

The metabolic changes in serum between the pre and post groups were further examined using heat map analysis (Fig. 3A). A general downregulation of carboxylic acids and derivatives was observed, with succinic acid and ethyl acetoacetate being particularly prominent. In addition, hydroxy fatty acids, including 3-hydroxybutyrate and 2-hydroxybutyrate, as well as sphingosine, were downregulated. These metabolites are linked to the tricarboxylic acid (TCA) cycle, ketone body-related fatty acid metabolism, and sphingolipid metabolism, respectively, and their decrease suggests a shift toward lower levels of intermediates commonly associated with energy demand and metabolic stress.

Metabolite profiling of saliva samples was conducted using UHPLC-Orbitrap-MS/MS to analyze metabolic changes induced by agro-healing activity. Differences between the pre and post groups in saliva were observed in the OPLS-DA plot, showing distinct separation in the negative ion mode of the UHPLC-Orbitrap-MS/MS (Fig. 2C), again indicating that the salivary metabolic profile was altered after the intervention.

Metabolites with VIP values of >1.0 from the OPLS-DA plots of saliva were selected for tentative identification. Based on the LC-MS results, 33 differential metabolites were identified, including 6 amino acids and their derivatives, 5 dipeptides, 7 carboxylic acids and their derivatives, 7 fatty acids and their derivatives, 3 purines and purine derivatives, 5 other metabolites, and 7 unidentified metabolites (Table 7). Heat map analysis of saliva metabolites (Fig. 3B) revealed an upregulation of histidine, tyrosine, lauroylglycine, malic acid, 2-ketoglutaric acid, 2,3-dihydroxybenzoic acid, salicylic acid, suberic acid, azelaic acid, sebacic acid, adipic acid, xanthine, and dimorphelic acid. Many of these metabolites are involved in amino acid metabolism, the TCA cycle, dicarboxylic acid metabolism, and purine metabolism, suggesting that agro-healing was associated with modulation of central energy- and amino acid-related pathways in saliva.

Pathway analysis of metabolic changes. Pathway analysis was conducted based on the identified metabolites. Among the pathways with a pathway impact >0.1 and $-\log_{10}(p) > 0.1$, the top five altered pathways were selected based on $-\log_{10}(p)$. In serum, these included α -linolenic acid metabolism, the citrate cycle (TCA cycle), glycerolipid metabolism, and glycine, serine, and threonine metabolism (Fig. 4A). In saliva, the altered pathways were phenylalanine, tyrosine, and tryptophan biosynthesis, tyrosine metabolism, histidine metabolism, arginine and proline metabolism, and the TCA cycle (Fig. 4B). Notably, the TCA cycle was identified as a common metabolic pathway altered in both serum and saliva,

indicating that agro-healing was associated with coordinated changes in central energy metabolism across systemic (serum) and oral (saliva) compartments.

Discovery of potential biomarker via ROC curve analysis. To identify potential biomarkers influenced by agro-healing activity, an ROC curve was generated, and the AUC was calculated to assess the accuracy of the model. Sphingosine was identified as a potential biomarker in serum samples. Sphingosine exhibited fair accuracy, with an AUC of 0.735 and a 95% confidence interval ranging from 0.58 to 0.886. The box-and-whisker plot of sphingosine demonstrated a decreasing trend in the post group compared with the pre group, and the independent *t* test *P* value was 0.0541 (Fig. 4C). Taken together, these findings suggest that sphingosine, a bioactive lipid involved in sphingolipid metabolism, may reflect agro-healing-related changes in serum lipid signaling, although the discriminative performance is modest and exploratory.

Discussion

This study evaluated a short plant-mediated agro-healing program for adults screened for elevated perceived stress. Through 8 sessions, participants showed reductions in depression, perceived stress, and anxiety alongside improvements in psychological flexibility, self-esteem, and life satisfaction. This pattern aligns with prior work linking stress exposure to burnout processes and self-esteem to protection against exhaustion (Awa et al. 2010; Cherniss 1980; Kang 2011). Conceptually, chronic stress can deplete coping resources and

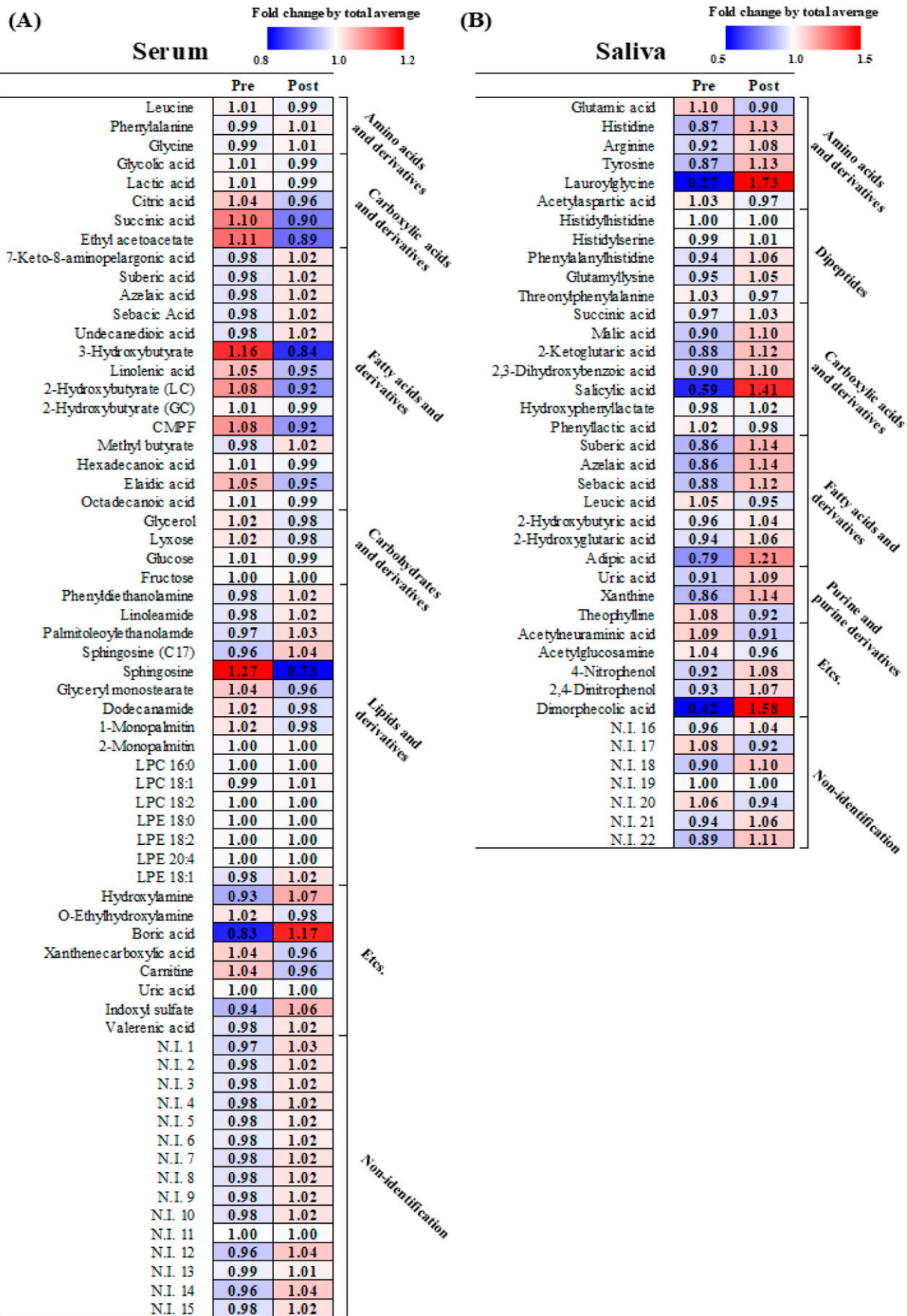


Fig. 3. Heat map analysis of the relative abundance of differential metabolites. (A) Serum metabolites identified using ultra-high performance liquid chromatography (UHPLC)-Orbitrap-tandem mass spectrometry (MS/MS) and gas chromatography-time-of-flight-mass spectrometry (GC-TOF-MS). (B) Saliva metabolites identified using UHPLC-Orbitrap-MS/MS. CMPF = 3-carboxy-4-methyl-5-propyl-2-furanpropionate; LC = liquid chromatography; N.I. = not identified.

Table 7. Significantly different metabolites in saliva identified by UHPLC-Orbitrap-MS/MS between pre and post groups.

| No. | Tentative identification ⁱ | VIP | Retention time (min) | Precursor ion (<i>m/z</i>) ⁱⁱ | MS fragments (<i>m/z</i>) ⁱⁱⁱ | Adduct | Exact mass | Formula | Error (ppm) | ID |
|----------------------------------|---------------------------------------|-------|----------------------|--|--|-----------------------|------------|---|-------------|--|
| Amino acids and derivatives | | | | | | | | | | |
| 1 | Glutamic acid | 1.39 | 0.78 | 146.046 | 102.056, 128.035, 127.051 | [M - H] ⁻ | 147.153 | C ₅ H ₉ NO ₄ | 0.43 | Lib. ⁱⁱⁱ MoNA ^{iv} |
| 2 | Histidine | 2.72 | 0.70 | 154.063 | 137.036, 93.046, 110.072 | [M - H] ⁻ | 155.070 | C ₆ H ₉ N ₃ O ₂ | 1.06 | MoNA |
| 3 | Arginine | 1.67 | 0.69 | 173.104 | 131.083, 156.078, 132.086 | [M - H] ⁻ | 174.112 | C ₈ H ₁₄ N ₄ O ₂ | 0.89 | MoNA |
| 4 | Tyrosine | 1.34 | 0.95 | 180.067 | 163.040, 119.050, 72.009 | [M - H] ⁻ | 181.074 | C ₉ H ₁₁ NO ₃ | -0.83 | MoNA |
| 5 | Lauroylglycine | 2.13 | 10.33 | 256.192 | 74.025, 116.929, 212.202 | [M - H] ⁻ | 257.199 | C ₁₄ H ₂₇ NO ₃ | 0.06 | MS ^v |
| 6 | Acetylaspartic acid | 2.29 | 0.95 | 174.041 | 88.040, 130.051, 94.030 | [M - H] ⁻ | 175.048 | C ₆ H ₉ NO ₅ | -0.93 | Lib, MoNA |
| Dipeptides | | | | | | | | | | |
| 7 | Histidylhistidine | 1.86 | 0.63 | 291.121 | 154.062, 110.072, 153.078 | [M - H] ⁻ | 292.128 | C ₁₂ H ₁₆ N ₆ O ₃ | -0.17 | MS |
| 8 | Histidylserine | 1.56 | 0.66 | 241.094 | 211.084, 167.094, 154.062 | [M - H] ⁻ | 242.101 | C ₉ H ₁₄ N ₄ O ₄ | -0.59 | MoNA |
| 9 | Phenylalanylhistidine | 2.34 | 0.98 | 301.130 | 154.062, 257.141, 110.072 | [M - H] ⁻ | 302.138 | C ₁₅ H ₁₈ N ₄ O ₃ | -0.91 | MS |
| 10 | Glutamyllysine | 1.45 | 0.64 | 274.141 | 145.098, 256.130, 212.140 | [M - H] ⁻ | 275.148 | C ₁₁ H ₂₁ N ₃ O ₅ | -0.13 | MS |
| 11 | Threonylphenylalanine | 1.81 | 1.29 | 265.119 | 221.093, 73.041, 164.072 | [M - H] ⁻ | 266.127 | C ₁₃ H ₁₈ N ₂ O ₄ | -0.44 | MS |
| Carboxylic acids and derivatives | | | | | | | | | | |
| 12 | Succinic acid | 1.23 | 1.05 | 117.019 | 73.029, 99.009, 55.019 | [M - H] ⁻ | 118.027 | C ₄ H ₆ O ₄ | 0.53 | Lib, MoNA |
| 13 | Malic acid | 2.71 | 0.89 | 133.014 | 115.004, 71.014, 89.025 | [M - H] ⁻ | 134.022 | C ₄ H ₆ O ₅ | 0.04 | Lib, MoNA |
| 14 | 2-Ketoglutaric acid | 1.95 | 0.94 | 145.014 | 101.024, 57.035, 74.025 | [M - H] ⁻ | 146.022 | C ₅ H ₆ O ₅ | 0.04 | MoNA |
| 15 | 2,3-Dihydroxybenzoic acid | 1.67 | 5.56 | 153.020 | 109.030, 154.023, 110.033 | [M - H] ⁻ | 154.027 | C ₇ H ₆ O ₄ | 0.40 | Lib, MoNA |
| 16 | Salicylic acid | 2.89 | 7.31 | 137.025 | 93.035, 138.020, 108.022 | [M - H] ⁻ | 138.032 | C ₇ H ₆ O ₄ | 1.09 | Lib |
| 17 | Hydroxyphenyllactate | 2.52 | 2.01 | 181.051 | 163.040, 181.992, 135.045 | [M - H] ⁻ | 182.058 | C ₉ H ₁₀ O ₄ | -0.10 | Lib |
| 18 | Phenyllactic acid | 1.18 | 6.38 | 165.056 | 147.045, 119.050, 72.993 | [M - H] ⁻ | 166.063 | C ₉ H ₁₀ O ₃ | -0.60 | Lib, MoNA |
| Fatty acids and derivatives | | | | | | | | | | |
| 19 | Suberic acid | 1.49 | 6.26 | 173.082 | 111.082, 129.092, 85.947 | [M - H] ⁻ | 174.089 | C ₈ H ₁₄ O ₄ | -0.49 | MoNA |
| 20 | Azelatic acid | 3.17 | 6.95 | 187.097 | 125.097, 169.087, 126.101 | [M - H] ⁻ | 188.105 | C ₉ H ₁₆ O ₄ | -0.75 | MoNA |
| 21 | Sebacic acid | 1.14 | 7.53 | 201.113 | 139.113, 183.103, 140.116 | [M - H] ⁻ | 202.120 | C ₁₀ H ₁₈ O ₄ | -0.29 | MoNA |
| 22 | Leucic acid | 1.80 | 5.81 | 131.072 | 85.066, 56.014, 113.061 | [M - H] ⁻ | 132.079 | C ₆ H ₁₂ O ₃ | 0.80 | MS |
| 23 | 2-Hydroxybutyric acid | 1.57 | 1.10 | 103.040 | 57.035, 59.014, 104.043 | [M - H] ⁻ | 104.047 | C ₄ H ₈ O ₃ | 0.84 | MoNA |
| 24 | 2-Hydroxyglutaric acid | 5.55 | 1.01 | 147.030 | 129.019, 103.040, 85.030 | [M - H] ⁻ | 148.037 | C ₇ H ₈ O ₅ | 0.18 | Lib |
| 25 | Adipic acid | 1.45 | 1.54 | 145.051 | 101.061, 83.050, 127.040 | [M - H] ⁻ | 146.058 | C ₆ H ₁₀ O ₄ | 0.61 | Lib, MoNA |
| Purines and pyrimidines | | | | | | | | | | |
| 26 | Uric acid | 18.29 | 0.89 | 167.021 | 124.015, 96.020, 168.025 | [M - H] ⁻ | 168.028 | C ₅ H ₄ N ₄ O ₃ | -0.77 | Lib, MoNA |
| 27 | Xanthine | 2.00 | 1.00 | 151.026 | 108.020, 152.029, 41.999 | [M - H] ⁻ | 152.033 | C ₅ H ₄ N ₄ O ₂ | 0.03 | MoNA |
| 28 | Theophylline | 2.04 | 1.31 | 179.057 | 134.988, 164.034, 75.009 | [M - H] ⁻ | 180.065 | C ₇ H ₈ N ₄ O ₂ | -0.17 | Lib |
| Other | | | | | | | | | | |
| 29 | Acetylneuraminic acid | 6.77 | 0.80 | 308.099 | 87.009, 170.046, 98.061 | [M - H] ⁻ | 309.106 | C ₁₁ H ₁₉ NO ₉ | 0.16 | MoNA |
| 30 | Acetylglucosamine | 2.32 | 0.80 | 256.059 | 119.035, 101.024, 59.014 | [M + Cl] ⁻ | 221.090 | C ₈ H ₁₂ NO ₆ | -0.88 | MoNA |
| 31 | 4-Nitrophenol | 1.10 | 7.43 | 138.020 | 93.035, 108.022, 137.025 | [M - H] ⁻ | 139.027 | C ₆ H ₅ NO ₃ | 1.79 | MS |
| 32 | 2,4-Dinitrophenol | 1.16 | 8.11 | 183.005 | 153.007, 123.009, 184.008 | [M - H] ⁻ | 184.012 | C ₆ H ₄ N ₂ O ₅ | 0.17 | MoNA |
| 33 | Dimorphelic acid | 2.65 | 10.99 | 295.228 | 277.217, 195.139, 171.103 | [M - H] ⁻ | 296.235 | C ₁₈ H ₃₂ O ₃ | 0.02 | MoNA |
| Not identified | | | | | | | | | | |
| | N.I. 16 | 1.59 | 1.46 | 115.040 | 115.921, 71.050, 44.998 | | | | | |
| | N.I. 17 | 1.61 | 1.47 | 291.098 | 127.051, 247.109, 185.057 | | | | | |
| | N.I. 18 | 3.81 | 4.06 | 172.098 | 172.991, 93.035, 111.082 | | | | | |
| | N.I. 19 | 3.85 | 4.12 | 172.991 | 93.035, 111.082, 79.957 | | | | | |
| | N.I. 20 | 1.15 | 5.94 | 277.156 | 130.087, 141.103, 91.055 | | | | | |
| | N.I. 21 | 2.96 | 7.18 | 214.145 | 197.118, 153.129, 215.129 | | | | | |
| | N.I. 22 | 1.50 | 7.68 | 228.161 | 211.134, 167.144, 229.144 | | | | | |

ⁱ Identified compounds based on the VIP value (>1.0) from the OPLS-DA model in Figure 1D.

ⁱⁱ Mass fragment patterns detected in negative mode.

ⁱⁱⁱ Mass spectrum compared with in-house libraries.

^{iv} Spectra matched to MassBank of North America.

^v Mass spectrum compared with PubChem and HMDB database.

MS = mass spectrometry; MS/MS = tandem mass spectrometry; N.I. = not identified; OPLS-DA = orthogonal partial least squares-discriminant analysis; UHPLC = ultra-high performance liquid chromatography; VIP = variable importance in the projection.

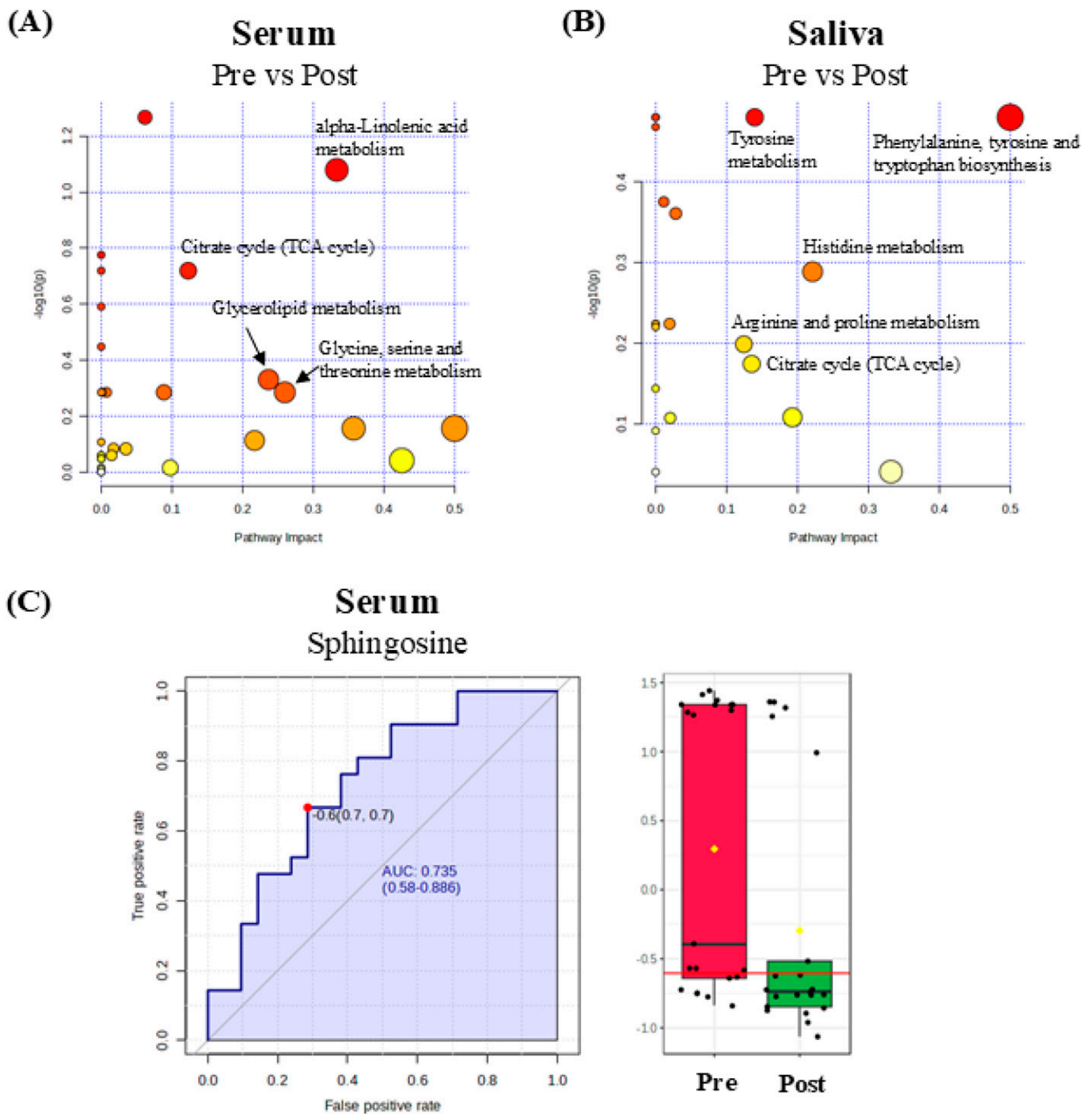


Fig. 4. Pathway analysis and biomarker evaluation of altered metabolites. (A, C) Pathway analysis of the altered metabolites in serum (A) and saliva (C) based on Kyoto Encyclopedia of Genes and Genomes pathway networks. (B) Receiver operating characteristic (ROC) curves and box-and-whisker plots of potential metabolite biomarkers (area under the ROC curve > 0.7) distinguishing the pre and post groups. TCA = tricarboxylic acid.

promote emotional exhaustion; the observed gains in psychological flexibility are consistent with acceptance- and mindfulness-based approaches that bolster resilience and reduce vulnerability to stress (Bond et al. 2011; Hayes et al. 2011).

The literature on plant-mediated agro-healing and related nature-based programs documents benefits for depression, anxiety, and general well-being (Murray et al. 2019; Song et al. 2010), with clinical samples also showing improvement (Gonzalez et al. 2011). Extending this work, our results provide preliminary

evidence that a brief, plant-mediated agro-healing program that combines structured horticultural tasks with simple reflective and mindfulness practices can improve mental health and well-being indicators in a screened, nonclinical adult sample. We intentionally refrained from labeling participants as “at risk of burnout” given the absence of a diagnostic classification and the ICD-11 position of burn-out as an occupational phenomenon rather than a medical diagnosis. Nevertheless, the intervention was explicitly framed as a burnout-related risk reduction program,

targeting stress-related risk factors within the JD-R framework while supporting psychological flexibility and broader self-regulatory capacities. Participants’ qualitative feedback emphasized the value of a structured, instructor-led format and peer interaction, supporting the role of guided, community-based delivery in sustaining engagement.

Beyond self-report outcomes, untargeted metabolomics yielded complementary insights. Serum and saliva profiles exhibited shifts across amino acids, fatty acids, carboxylic acids, and lipid derivatives. In serum, we

observed downregulation of hydroxy fatty acids and sphingosine—molecules implicated in energy and lipid-signaling pathways—while saliva showed increases in histidine, tyrosine, and several carboxylic acids. Pathway analysis indicated modulation of the TCA cycle in both matrices, compatible with, rather than proving, shifts in cellular energy metabolism that are often reported alongside affective symptomatology (Zhang et al. 2011). These observations mirror prior reports of elevated 3-hydroxybutyrate and related fatty acids in stress and depression (Hadrévi et al. 2019; Setoyama et al. 2016); the postintervention decreases we observed are directionally consistent with a restorative change. Likewise, increases in amino-acid-related metabolites (phenylalanine/tyrosine/histidine; arginine/proline pathways) are congruent with potential normalization of stress-perturbed neurotransmitter/immune-linked processes (Morgan et al. 2022). Overall, the reversal of metabolite patterns typically associated with stress suggests that agro-healing activity may contribute to metabolic normalization and stress alleviation. Notably, sphingosine emerged as a candidate biomarker with fair discrimination (AUC \approx 0.74) and lower postintervention levels. Given the untargeted workflow and small sample, this signal should be regarded as hypothesis-generating; targeted quantification and preregistered validation cohorts will be required to establish robustness and interpretability.

Taken together, the convergence of psychological improvements and plausible metabolic shifts supports an integrative psychophysiological account in which a plant-mediated agro-healing program, enriched by brief mindfulness and reflective practices, may promote stress recovery and metabolic homeostasis. Notwithstanding its limitations, the approach tested in this study suggests that even a brief intervention can contribute to enhanced psychological flexibility and stress reduction in adults with elevated perceived stress. Because it is grounded in low-intensity plant-care and farm-related activities that can be delivered in small groups, this model of plant-mediated agro-healing program is relatively accessible and adaptable to community and workplace settings, thereby aligning with the preventive aims articulated in the introduction concerning rising stress and burnout risk. In light of increasing work-related stress and burnout globally, scalable interventions that jointly target cognitive-emotional processes and somatic regulation are needed; plant-mediated agro-healing with simple psychological practices appears to be a feasible, accessible, and potentially cost-effective option for such prevention strategies.

Future research should use randomized, adequately powered, preregistered designs with a priori primary endpoints (including a validated burnout scale), larger and more diverse samples, and longer follow-up to test durability and potential dose-response effects. Studies should apply rigorous multiple-comparison control, employ targeted metabolite assays, and pursue external validation of candidate biomarkers/

metabolomic signatures. Finally, multisite trials built on a standardized core protocol with context-specific adaptations are needed to establish generalizability across settings and populations. As this evidence base expands, plant-mediated agro-healing programs that incorporate low-intensity psychological components could evolve into integrative interventions that foster psychological recovery and support metabolic homeostasis in adults chronically exposed to high stress or at risk for burnout, strengthening their potential as multidimensional, preventive models for mitigating stress-related risk factors.

Future directions. Future studies should recruit larger, more diverse samples to improve precision and generalizability. Validated burnout measures should be included alongside perceived stress screening to directly test burnout-prevention effects and determine whether benefits extend beyond stress-related outcomes in nonclinical samples. Randomized controlled trials with appropriate comparators and follow-up assessments are needed to strengthen causal inference and reduce threats such as regression to the mean, expectancy effects, time-related confounding, and unmeasured cointerventions. Although tailored session content may enhance relevance, future work should evaluate the balance between personalization and standardization and test whether core components generalize across settings and populations. Metabolomics results should be confirmed in adequately powered studies using prespecified hypotheses, multiplicity control, and targeted assays; in particular, sphingosine-related signals should be replicated in independent samples before inferring biomarker potential.

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