**File S1 Participant’s inclusion and exclusion criteria**

As previous studies using large populations demonstrated that the standard treatment options of low dosages of prednisone and hydroxychloroquine are not associated with gut microbiome composition\(^1,\,2\), patients using low dosages of these two medications were included. The exclusion criteria for both cohorts were presence of other autoimmune diseases, pregnancy, breastfeeding, menstruation, severe illness or infections, neoplastic disease, or use of antibiotics, probiotics, vitamin D, vitamin B12, calcium, oral contraceptive, metformin, or proton pump inhibitors within the 2 weeks prior to participation in the study. Night shift subjects also were excluded. At the time of sample collection, controls declared that they had no health problems and that they were not taking medications.

**REFERENCES**

1. Jackson M, Verdi S, Maxan M, Shin C, Zierer J, Bowyer R, Martin T, Williams F, Menni C, Bell JT, Spector T, Steves C. 2018. Gut microbiota associations with common diseases and prescription medications in a population-based cohort. Nat Commun 9:2625. 10.1038/s41467-018-03184-7.
2. Zhernakova A, Kurilshikov A, Bender M, Tigchelaar E, Schirmer M, Vatanen T, Mujagic Z, Vila A, Falony G, Vieira-Silva S, Wang J, Imhann F, Brandts E, Jankipersadsing S, Joossens M, Cenit M, Deelen P, Swertz M, Weersma R, Feskens E, Netea M, Gevers D, Jonkers D, Franke L, Anichenko Y, Huttenhower C, Raes J, Hofker M, Xavier R, Wijmenga C, Fu J. 2016. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. Science 352:565-569. 10.1126/science.aad3369.
File S2 Nutrient intake

A Chinese version of the food frequency questionnaire (FFQ) was used to assess food intake during a face-to-face interview (1). The participants were asked to recall their food and water intake patterns over the previous year (up to the day of urine sample collection). The name and amount consumed food was assessed as was the intake of nutrition supplements. Haoyingyang sofware v. 2.08.07 (Pinwang inc. ShenZhen, China) was used to convert the amount of food intake into daily nutrient intake.

REFERENCES

1. Zhao WH, Huang ZP, Zhang X, He L, Willett W, Wang JL, Hasegawa K, Chen JS. 2010. Reproducibility and validity of a chinese food frequency questionnaire. Biomed Environ Sci:1-38.
**File S3 DNA extraction and sequence**

Each 30 mL urine sample was centrifuged at 10,000×g for 30 min at 4°C. Most of the supernatant fluid was decanted, and the pellet was resuspended in the remaining 1 mL of urine transferred to a 1.5 mL Eppendorf tube at 10,000×g for 30 min at 4°C. The supernatant was gently removed and 500 μL lysis buffer (Guhe, Hangzhou, China) was added. The samples were repeatedly frozen and thawed in liquid nitrogen and a 65°C water bath for 3 cycles. AMPure XP magnetic beads (Beckman Coulter, Indianapolis, IN, USA) were used to isolate bacterial DNA. Specifically, 40 μL Agencourt AMPure XP (Beckman Coulter, USA) was added to 80 μL of the urine pellet, vortexed for 30 sec, and incubated for 5 min at room temperature. The tube was placed into a magnetic separator for 5 min, and DNA was bound to magnetic beads, which were drawn to the wall of the microcentrifuge tube. The supernatant was carefully removed without disrupting the magnetic beads. The sample was washed twice with 180 μL 80% ethanol for 30 sec, being placed on a magnet separator between each washing. The purified DNA was eluted with 30 μL elution buffer for 1 min. The beads, now released from the DNA, were collected with the magnet. The DNA-containing supernatant was transferred to a clean tube. Two samples with sterile deionized water were used as negative controls to assess the reagent contamination at this step.

The bacterial 16S rRNA V3-V4 region was PCR-amplified using the universal primers 319F and 806R with 32 cycles. Two samples of sterile water were used to assess reagent contamination. The quantity and quality of the extracted DNA were measured using a NanoDrop ND-1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) and agarose gel electrophoresis, respectively. PCR amplicons were purified with Agencourt AMPure XP Beads (Beckman Coulter, Indianapolis, IN, USA) and quantified using the PicoGreen dsDNA Assay Kit (Invitrogen, Carlsbad, CA, USA). Amplicons were then pooled in equal amounts for sequencing using the Illumina MiSeq platform samples. Two samples without PCR product were sequenced to assess cross contamination.

As low bacterial DNA biomass in urine samples, we assessed potential bacterial
and DNA contamination in the environment using 21 negative samples. They were as follows: air in the biosafety cabinet, various tubes used in the sample collection and DNA isolation, urinary catheter, and reagent. Each type was collected using three samples. For each instrument used in our study, triplicate samples were sequenced as negative controls. For example, three urinary catheters were placed in a sterile cell culture plate. A sterile scissors was used to cut a 1 mM portion of catheter, which was placed in 500 µL lysis buffer. The lysis buffer containing catheters was then processed as described for urine samples. The negative samples were processed with the urine samples immediately and were not exposed biosafety cabinet air for a long time.
File S4 Urinary metabolites processing

Urinary metabolome profiling was performed using liquid chromatography tandem mass spectrometry, LC-MS/MS (ExionLC and TripleTOF 5600, SCIEX, Framingham, MA, USA) as previously described (1). Briefly, 20 μL urine was used for metabolite extraction with 120 μL of precooled 50% methanol. After vortexing for 1 min, the extraction mixture was incubated at room temperature for 10 min and then stored overnight at -20°C. After centrifugation at 4,000 × g for 20 min, the supematants were transferred into 96-well plates and then stored at -80°C prior to LC-MS analysis. Meanwhile, pooled quality control samples were prepared by combining 10 μL of each extraction mixture. Features detected in less than 50% of QC samples or 80% of the urine samples were removed, and the remaining peaks with missing values were imputed with the k-nearest neighbor algorithm to further improve data quality.

REFERENCES

1. Xiang S, Ye K, Li M, Ying J, Wang H, Han J, Shi L, Xiao J, Shen Y, Feng X, Bao X, Zheng Y, Ge Y, Zhang Y, Liu C, Chen J, Chen Y, Tian S, Zhu X. 2021. Xylitol enhances synthesis of propionate in the colon via cross-feeding of gut microbiota. Microbiome 9. 10.1186/s40168-021-01029-6.
Supplementary Figures

Fig. S1 Overview of the study design.

Fig. S2 Medication usages in patients didn’t affect bladder microbiome.
A. PCoA based on Bray-Curtis distances at species level did not show different microbial compositions between SLE patients taking hydroxychloroquine dosages of 0.2 mg/d and those taking 0.4 mg/d. Permutational multivariate analysis of variance (PERMANOVA) was performed for statistical comparisons of samples using different levels of hydroxychloroquine. P value was adjusted by Benjamini and Hochberg false discovery rate.

B. PCoA based on Bray-Curtis distances at species level did not show different microbial compositions among SLE patients taking prednisone of 0 mg/d, 5 mg/d and those taking 10 mg/d. PERMANOVA was performed for statistical comparisons of samples using different levels of prednisone. P value was adjusted by Benjamini and Hochberg false discovery rate.

Fig. S3 Bacterial evenness and richness of bacterial diversity.
A. Comparison of bacterial species diversity indicator of evenness between control and SLE groups. Permutational multivariate analysis of variance (PERMANOVA) was performed for statistical comparisons of samples in two groups. P value was adjusted by Benjamini and Hochberg false discovery rate. ** indicates $P_{adj} < 0.01$.

B. Comparison of bacterial species diversity indicator of richness between control and SLE groups. PERMANOVA was performed for statistical comparisons of samples in two groups. P value was adjusted by Benjamini and Hochberg false discovery rate.

Fig. S4 Bacterial communities and composition at bacterial genus level.
A. PCoA based on Bray-Curtis distances at the genus level showed different microbial compositions between control and SLE groups. Permutational multivariate analysis of variance (PERMANOVA) was performed for statistical comparisons of samples in two groups. \( P \) value was adjusted by Benjamini and Hochberg false discovery rate.

B. Heatmap of bacterial genera. The 15 abundant genera (>1% average relative abundances) were displayed.

**Fig. S5** Bacterial composition at bacterial species level.

The heatmap displays the bacterial species >0.5% average relative abundances.

**Fig. S6** Comparison of bladder microbiome among control, LN and non-LN groups.

A. Bacterial communities among controls, LN and non-LN SLE patients. PCoA based on Bray-Curtis distances at species level was performed. Permutational multivariate analysis of variance (PERMANOVA) was performed for statistical comparisons of samples in two groups. \( P \) value was adjusted by Benjamini and Hochberg false discovery rate.

B. Bacterial diversity measured by Shannon index was calculated at the bacterial species level. Wilcoxon rank-sum test and adjusted by Benjamini and Hochberg false discovery rate (FDR). ** indicates \( P_{(\text{adj})} < 0.01 \).

**Fig. S7** Comparison of microbiome in bladder, vagina, and gut in SLE patients.

A. PCoA based on Bray-Curtis distances at species level showed different microbial compositions between the bladder, vagina, and gut. (PERMANOVA) was performed for statistical comparisons of samples in two groups. \( P \) value was adjusted by Benjamini and Hochberg false discovery rate.
B. Bray-Curtis dissimilarities of the different niches were calculated using the same
SLE patient. Wilcoxon rank-sum test and adjusted by Benjamini and Hochberg false
discovery rate (FDR). **, *** indicate $P_{(adj)} < 0.01$ and $P_{(adj)} < 0.001$, respectively.

C. Microbial profiles of the bladder, gut, and vagina at the species level. Bacterial
species abundance with $>0.05\%$ average relative abundances are displayed. On the x
axis, the numbers 1 to 15 represent SLE patients with bladder urine, gut and vaginal
samples sequenced.

**Fig. S8** Medication usages in SLE patients didn’t affect urinary metabolome.

A. Principal component analysis (PCA) was used to compare urinary metabolome
between SLE patients taking hydroxychloroquine dosages of 0.2 mg/d and those
taking 0.4 mg/d. The explained variances are shown in brackets. Anosim was used to
calculate $R^2$ and $P$ value. The 95% confidence ellipse is drawn for each group.

B. Principal component analysis (PCA) was used to compare urinary metabolome
among SLE patients taking prednisone of 0 mg/d, 5 mg/d, and 10 mg/d. Anosim was
performed for statistical comparisons of samples in two groups. The 95% confidence
ellipse is drawn for each group.

**Fig. S9** Metabolome comparison between control and SLE groups.

A. Volcano plot. Volcano plot of differential metabolites classification of the
control and SLE groups. Metabolites with FDR $<0.05$ obtained by non-parametric
tests and fold change (FC) $>2$ were identified as significantly different between the
two groups. Colored plots indicate upward trend and downward trend of metabolites,
and gray plots indicate that they are not statistically significant.

B. Clustering result shown as heatmap. Distance was measured using Euclidean,
and clustering algorithm was calculated using Ward’s method.
Fig. S10 Metabolome comparison among control, LN and non-LN SLE groups.

Metabolome among controls, LN and non-LN SLE patients were compared using principal component analysis (PCA). Anosim was performed for statistical comparisons of samples between groups. The 95% confidence ellipse is drawn for each group.

Fig. S11 The relationship between bladder microbiome and urinary metabolome.

Procrustes analysis analyzed the congruence of two-dimensional shapes produced from superimposition of principal component analyses from the datasets of microbiome and metabolome. Euclidian distances of eigenvalues for both the microbiome and metabolome using the Procrustes function in the vegan R package. Longer lines on Procrustes plots indicate more within-subject dissimilarity of the microbiome and metabolome. Significance value shown was calculated using the protest function from the vegan R package.

Fig. S12 Urinary cytokines differed in LN SLE patients comparing to controls.

Comparison of urinary cytokines between controls and LN SLE patients. P value was calculated using Wilcoxon rank-sum test and adjusted by Benjamini and Hochberg false discovery rate. *, **, *** indicate \( P_{(adj)} < 0.05 \), \( P_{(adj)} < 0.01 \) and \( P_{(adj)} < 0.001 \), respectively.
Study cohort
Controls (n=50)
SLE (n=50)

sex-, age-, BMI-, and co-morbid disease-matched

Catheterized urine sample

Microbiome (sediment)

Metabolome (supernatant)

Cytokines (supernatant)

a. Identification of signatures of taxonomy, metabolome and cytokines
b. Taxa-metabolites, taxa-cytokines and taxa-disease profiles associations
Panel A: Evenness

Panel B: Richness
A. PCA (hydroxychloroquin dosage)

- PC 1: 19.7% of variation explained
- PC 2: 12.3% of variation explained

R = 0.027, P = 0.249

B. PCA (Prednisone dosage)

- PC 1: 20.9% of variation explained
- PC 2: 12% of variation explained

R = 0.002, P = 0.505
Legends of supplementary variables:

- Tab. 1: original serum for individual MLA
- Tab. 2: Determined bacterial protein and its relative abundance
- Tab. 3: Desirable bacterial species and its relative abundance
- Tab. 4: Assembleable metabolites
- Tab. 5: Differential metabolites
- Tab. 6: Distribution of male patients
- Tab. 7: Comparison of the condition between controls and SLE

Unidentified names in the supplementary appendix:

- Tab. 8: Patient’s characteristics
- Tab. 9: Unidentified names

Abbreviations:
- MLA: Microorganisms
- MLA: Multivariable regression with linear model
- PCA: Principal component analysis
- VIP: Variable importance in projection
- ROC: Receiver operating characteristic
- AUC: Area under the curve

Significant differences were determined using the Wilcoxon rank-sum test (for continuous variables) or Fisher’s exact test (for categorical variables). The Benjamini-Hochberg method was used to adjust for multiple comparisons. All analyses were performed using R software (version 3.6.3).
| Location | Name | Layer | Distance (mm) | Width (mm) | Height (mm) | Zn (+) | Cu (+) | Pb (+) | Textured | Other | Reference | Method | Error | Error |
|----------|------|-------|---------------|------------|-------------|--------|--------|--------|----------|-------|-----------|--------|-------|-------|
| GLS1     | Page | 36    | 1             | 4          | 6           | No     | No     | No     |          |       |           |        |       |       |
| GLS2     | Page | 45    | 2             | 4          | 6           | No     | No     | No     |          |       |           |        |       |       |
| GLS3     | Page | 55    | 1             | 4          | 6           | No     | No     | No     |          |       |           |        |       |       |
| GLS4     | Page | 65    | 2             | 4          | 6           | No     | No     | No     |          |       |           |        |       |       |
| GLS5     | Page | 75    | 1             | 4          | 6           | No     | No     | No     |          |       |           |        |       |       |

*Notes: NaN represents not applicable. The symbols indicate the presence or absence of features: + for a feature present, - for a feature absent. Method: 1 = In-situ XRF, 2 = remote sensing.
### Tab. S7 Comparison of nutrient intake between controls and SLE

| Nutrient intake   | Controls (n = 50)     | SLE (n = 50)       | P value |
|-------------------|-----------------------|--------------------|---------|
| Calcium (mg/d)    | 430.81 ± 256.02       | 1223.33 ± 472.72   | < 0.001 |
| Carbohydrate (g/d)| 247.50 ± 73.32        | 217.64 ± 78.79     | 0.053   |
| Carotene (µg/d)   | 17.59 ± 4.22          | 20.1 ± 8.40        | 0.063   |
| Cholesterol (mg/d)| 527.42 ± 188.43       | 516.16 ± 235.38    | 0.792   |
| Copper (mg/d)     | 2.20 ± 0.65           | 2.06 ± 1.12        | 0.478   |
| Energy (Kcal/d)   | 2191.03 ± 308.2       | 2048.09 ± 478.82   | 0.080   |
| Fat (g/d)         | 116.62 ± 149.62       | 97.52 ± 46.84      | 0.391   |
| Fiber (g/d)       | 12.04 ± 8.59          | 13.93 ± 8.34       | 0.269   |
| Iron (mg/d)       | 30.31 ± 16.64         | 25.14 ± 16.05      | 0.117   |
| Magnesium (mg/d)  | 243.91 ± 76.91        | 277.58 ± 94.16     | 0.053   |
| Manganese (mg/d)  | 5.77 ± 2.63           | 5.03 ± 2.44        | 0.147   |
| Niacin (mg/d)     | 15.78 ± 4.46          | 17.7 ± 6.39        | 0.084   |
| Phosphorus (mg/d) | 776.72 ± 195.95       | 843.82 ± 304.34    | 0.194   |
| Potassium (mg/d)  | 1667.48 ± 579.82      | 1874.99 ± 547.99   | 0.069   |
| Protein (g/d)     | 69.53 ± 18.34         | 80.64 ± 41.53      | 0.088   |
| Retinol (µg/d)    | 1004.76 ± 299.76      | 1121.91 ± 378.41   | 0.089   |
| Selenium (mg/d)   | 44.24 ± 16.67         | 49.00 ± 20.69      | 0.208   |
| Sodium (mg/d)     | 2207.3 ± 416.01       | 2401.04 ± 664.25   | 0.084   |
| Vitamin A (µg/d)  | 1106.72 ± 518.13      | 1398.03 ± 908.65   | 0.052   |
| Vitamin B1 (mg/d) | 0.82 ± 0.39           | 0.97 ± 0.43        | 0.076   |
| Vitamin B2 (mg/d) | 1.27 ± 0.6            | 1.48 ± 0.61        | 0.073   |
| Vitamin C (mg/d)  | 84.93 ± 39.66         | 99.05 ± 52.96      | 0.135   |
| Vitamin E (mg/d)  | 66.66 ± 12.77         | 60.48 ± 23.79      | 0.110   |
| Zinc (mg/d)       | 9.71 ± 3.55           | 11.49 ± 4.19       | 0.024   |

Student's t test on normalized continuous variables and Wilcoxon rank-sum test was used on un-normalized continuous variables.
| Variable     | Taxonomy | Coefficient | p value  | p (adj) value |
|--------------|----------|-------------|----------|---------------|
| Calcium      | Bacteria | 0.000       | 0.002    | 0.027         |
|              | Aragonite | 0.000       | 0.002    | 0.013         |
| Potassium    | Bacteria | 0.010       | 0.010    | 0.010         |

*Table 2: Bacterial taxonomy, affected by food intake.*
| Parameters | Control (n = 58) | LN (n = 35) | non-LN (n = 12) | Value for subset (n x 0.5) or statistics |
|-----------|-----------------|-------------|-----------------|------------------------------------------|
| Female sex, n (%) | 44 (88) | 31 (88.6) | 9 (75.0) | 0.520 | 0.521 | 0.141 |
| Age (yr) | 49.23 ± 17.16 | 31.03 ± 15.45 | 54.42 ± 16.66 | 0.003 | 0.389 | 0.009 |
| Duration of SLE (yr) | NA | 8.06 ± 6.12 | 10.03 ± 6.57 | NA | NA | 0.143 |
| SLEDAI | NA | 16.05 ± 1.68 | 9.42 ± 2.12 | NA | NA | 0.002 |
| Duration of LN (yr) | NA | 5.10 ± 3.50 | NA | NA | NA | NA |
| Body-mass index (kg/m²) | 23.85 ± 3.23 | 24.29 ± 2.84 | 22.60 ± 1.72 | 0.020 | 0.045 | 0.127 |
| Comorbidities | | | | | | |
| Diabetes, n (%) | 2 (0.9) | 4 (10.5) | 1 (8.3) | 0.056 | 0.100 | 0.000 |
| Hypertension, n (%) | 10 (20) | 9 (26.4) | 1 (8.3) | 0.677 | 0.342 | 0.246 |
| Hematological/immunological features | | | | | | |
| Complement 3 (g/L) | 1.20 ± 0.64 | 0.74 ± 0.24 | 1.34 ± 0.87 | -0.100 | 0.061 | 0.194 |
| Complement 4 (g/L) | 0.39 ± 0.10 | 0.15 ± 0.06 | 1.17 ± 0.03 | -0.001 | 0.002 | 0.113 |
| Ig A (g/L) | 2.98 ± 0.53 | 2.85 ± 1.15 | 2.04 ± 0.46 | 0.331 | 0.381 | 0.333 |
| Ig G (g/L) | 10.85 ± 3.51 | 16.44 ± 4.72 | 14.49 ± 2.04 | 0.003 | 0.007 | 0.009 |
| Ig M (g/L) | 1.17 ± 0.51 | 2.03 ± 0.56 | 0.95 ± 0.20 | 0.158 | 0.352 | 0.870 |
| ESR (mm/hr) | NA | 32.46 ± 24.27 | 21.48 ± 4.39 | NA | NA | 0.187 |
| renal function | | | | | | |
| Serum creatinine (umol/L) | 55.25 ± 16.75 | 61.65 ± 16.31 | 71.81 ± 67.75 | 0.174 | 0.346 | 0.504 |
| Blood urea nitrogen (mmol/L) | 7.75 ± 2.59 | 7.66 ± 2.23 | 5.47 ± 1.50 | 0.341 | 0.386 | 0.743 |
| Serum uric acid (umol/L) | 461.04 ± 72.56 | 327.97 | 290.53 ± 82.75 | 0.014 | 0.411 | 0.209 |
| Estimated glomerular filtration rate (mL/min/1.73 m²) | 114.41 ± 19.08 | 111.09 ± 18.53 | 101.29 ± 19.15 | 0.652 | 0.292 | 0.482 |
| Urinary creatinine (umol/L) | 123.91 ± 17.13 | 15.65 ± 18.25 | 121.17 ± 32.26 | 0.014 | 0.980 | 0.000 |
| Other analyses | | | | | | |
| White blood cells (x10⁹/L) | 2.22 ± 0.38 | 18.63 ± 25.06 | 5.16 ± 10.06 | -0.001 | 0.002 | 0.799 |
| Red blood cells (x10¹²/L) | 0.61 ± 0.03 | 26.83 ± 45.84 | 25.55 ± 73.65 | -0.001 | 0.081 | 0.551 |
| Nitrates positive (%) | 3 (5) | 6 (18.1) | 2 (16.7) | 0.370 | 1.000 | 1.000 |
| LACTIC ACID DEHYDROGENASE (%) | 0 (0) | 11 (32.9) | 12 (31.2) | -0.001 | 0.244 | 0.145 |

* p < 0.05; ** p < 0.01; *** p < 0.001

Abbreviations: LN, lupus nephritis; NA, not applicable; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.
| Year | Date       | Event                      | Location |
|------|------------|----------------------------|----------|
| 1965 | July 25    | Apollo 11 launch           | Kennedy Space Center |
| 1969 | July 20    | Apollo 11 moon landing     | Kennedy Space Center |
| 1971 | July 20    | Apollo 15 moon landing     | Kennedy Space Center |
| 1972 | July 19    | Apollo 16 moon landing     | Kennedy Space Center |
| 1972 | July 20    | Apollo 17 moon landing     | Kennedy Space Center |

Note: This table contains important dates for space missions and the locations where they occurred.
| Metabolite                                                                 | VIP     |
|--------------------------------------------------------------------------|---------|
| 11-beta-Hydroxystrosterone-3-glucuronide                                  | 1.159   |
| 11-Methyl-7-oxatetraacyclo[6.2.1.01,6.04,11]dodeca-9E-ene               | 1.812   |
| 12-Hydroxy-13-O-D-glucuronoside-octadec-9Z-enolate                      | 1.111   |
| 16alpha-hydroxydehydroepiandrosterone-3-sulfate                          | 1.502   |
| 1H-Indole-1-carboxamide, 6-chloro-2,3-dihydro-5-methyl-N-[6-[(2-methyl-3-pyridinyl)oxy]-3-pyridinyl]- | 1.076   |
| 1'-Hydroxymidazolam, beta-D-glucuronide                                   | 3.258   |
| 3-Hydroxy-2-(4-methylbenzoyl)tetralin-4-one                              | 1.490   |
| 4,5-Dihydro-oxaepine-3-sulfate                                          | 1.209   |
| 5-alpha-androstan-3-beta-ol-17-one sulfates                              | 1.112   |
| 7,8-di hydroxy-2H-chromen-2-one                                          | 1.329   |
| Acesulfame                                                                | 1.033   |
| Acetyl-DL-carnitine                                                       | 1.002   |
| Acetylcarnitine 18:5                                                      | 1.409   |
| Acetylcarnitine 21:5                                                     | 1.726   |
| Androsterone glucuronide                                                 | 1.011   |
| Beazenesulfonic acid                                                     | 2.291   |
| Celastrol                                                                | 1.207   |
| Clozapine                                                                | 1.292   |
| Clozapine glucuronide                                                    | 1.266   |
| Codeine                                                                  | 1.130   |
| Cortolone-3-glucuronide                                                  | 1.167   |
| Cyclamete                                                                | 1.252   |
| cyclic N-Acetylserotonin glucuronide                                     | 2.029   |
| Desethylchloroquine                                                      | 1.455   |
| Diethyl sebacate                                                         | 1.018   |
| Gibberellin A92                                                          | 1.538   |
| Hydroxychloroquine                                                       | 2.094   |
| Lidocaine                                                                | 2.028   |
| LysoPA 19:2; LysoPA 19:2                                                 | 1.077   |
| Olepataladine                                                            | 1.799   |
| PC(16:0/16:1(9Z))                                                        | 1.464   |
| PG 18:0; PG(2.0/16:0)                                                    | 1.024   |
| PG 18:0; PG(9.0/9.0)                                                     | 1.002   |
| Flutretin                                                                | 1.666   |
| Propofol beta-D-glucuronide                                              | 3.799   |
| S-Adenosyl-L-methionine                                                  | 1.534   |
| Styrene                                                                  | 1.616   |
| Sulfamethazine                                                           | 2.419   |
| Taurineclobate                                                           | 1.627   |
| TG 36:6; TG(12:2/12:2/12:2)                                              | 1.384   |
| TG 48:10; TG(12:3/15:2/19:5)                                             | 1.582   |
| Tryptophyl-Phenylalanine                                                 | 1.666   |

VIP was calculated using PLS-DA analysis
Abbreviation VIP, Variable importance in Projection
| Column 1 | Column 2 | Column 3 | Column 4 | Column 5 |
|---------|---------|---------|---------|---------|
| Value 1 | Value 2 | Value 3 | Value 4 | Value 5 |

Note: The table contains data that could be interpreted in various ways depending on the context. The columns represent different variables or categories, and the values indicate the corresponding measurements or classifications.
| Metabolites                                                                 | 0.2 (mg/d) mean ± SD | 0.4 (mg/d) mean ± SD | \( P_{adj} \) value |
|----------------------------------------------------------------------------|----------------------|----------------------|-------------------|
| 11-beta Hydroxyaztreomycin 3-glucuronide                                    | 0.68±9.64            | 0.02±3.12            | 1.000             |
| 11-Methyl-7-spiroerythron[6,2.1.0,6.04.11]dodecanol                        | 54.4±6.74            | 5.5±5.5              | 1.000             |
| 12-Hydroxy-13-D-glucuronosyl-2-acetate                                      | 10.2±14.02           | 17.4±4.11            | 1.000             |
| 16-alpha-hydroxy-1-dihydrospidomicrosterc-2-sulfate                        | 261.5±3.24           | 353.3±45.16          | 1.000             |
| 18-Indole-1-carboxamic, 6-chloro-2,3-dihydr.-5-methyl-3-[6-[2-methyl-3-pyridyl]pyrrol]-3-pyridyl                                  | 10.3±5.3             | 8.1±3.2              | 1.000             |
| 1-Hydroxyaztreomycin, beta-D-glucuronide                                    | 1.05±0.5             | 1.03±0.5             | 1.000             |
| 3-Hydroxy-2-[4-methylbenzyl]-4H-1-benzopyran-4-one                          | 581.0±44.14          | 672.2±75.64          | 1.000             |
| 4.5-Dihydro-dipicolinom-3-sulfate                                          | 228.0±14.01          | 274.3±2.23           | 1.000             |
| 5-alpha-Acetamin-3-beta-o-17-est-sulfate                                    | 41.1±7.05            | 41.3±4.12            | 1.000             |
| 7-alpha-dihydropyrimidrazo-2-ene-6-oxide                                    | 10.7±5.21            | 20.0±9.12            | 1.000             |
| Acetylaminol                                                              | 94.4±20.04           | 206.7±5.68           | 1.000             |
| Acetil-DL-carnitina                                                        | 531.5±107.4          | 1211.1±2125.31       | 1.000             |
| Acetylcarnitina-1.5                                                        | 14.3±27.80           | 5.0±9.15             | 1.000             |
| Acetylcarnitina-1.5                                                        | 15.5±34.15           | 15.26±1.3            | 1.000             |
| Androsoruberine glucuronide                                                | 1777.1±1.834.14      | 2202.2±1.412.29      | 1.000             |
| Benzencesulfonic acid                                                       | 1.74±1.23            | 5.4±7.27             | 1.000             |
| Cisatrel                                                                   | 161.8±30.14          | 150.7±61.01          | 1.000             |
| Clozapine                                                                  | 1.45±45.04           | 2.6±66.73            | 1.000             |
| Clozapine-3-glucuronide                                                    | 17.0±6.12            | 21.44±7.78           | 1.000             |
| Codams                                                                    | 17.8±30.5            | 12.87±6.31           | 1.000             |
| Correlolona-3-glucuronide                                                  | 201.8±1005.21        | 1234.1±1572.55       | 1.000             |
| cyclic 4-Acetylacteamin glucuronide                                        | 42.7±11.47           | 45.6±13.68           | 1.000             |
| Dasetyl-benzylmethylocitrate                                               | 937.9±102.01         | 445.1±70.76          | 1.000             |
| Diallyl-carbazine                                                          | 10.1±47.87           | 120.77±60.15         | 1.000             |
| Gibbaretin A2                                                              | 14.8±63.13           | 13.36±67.74          | 1.000             |
| Hydroxy-chloroquinines                                                     | 221.3±443.72         | 203.4±231.66         | 1.000             |
| Lysergic acid 10.2,3-lysergic acid-10.3                                     | 71.3±60.84           | 98.8±81.4            | 1.000             |
| Clozapinol                                                                | 73.5±45.36           | 95.8±77.23           | 1.000             |
| EC(18,8,11,10,7)                                                          | 1301.6±206.64        | 2471.4±5478.25       | 1.000             |
| EG 18.8, RO(0,1,6,3)                                                       | 107.5±72.77          | 163.5±273.68         | 1.000             |
| EG 18.8, RO(0,0,3)                                                        | 154.8±159.27         | 174.5±230.53         | 1.000             |
| Ethanol                                                                   | 13.3±5.11            | 14.3±6.74            | 1.000             |
| 5.6-Anisyl-1-methanamin                                                    | 17.5±6.33            | 18.0±4.68            | 1.000             |
| Syntox                                                                      | 5.4±7.78             | 4.6±4.15             | 1.000             |
| Trimethoprim                                                              | 47.5±312.01          | 25.0±14.65           | 1.000             |
| TG 16:6, TG(12.3,12.0,13:2)                                                | 1045.6±366.62        | 3511.0±6133.34       | 1.000             |
| TG 46:0, TG(12:1,13:5,19:5)                                                | 965.8±2042.34        | 1634.3±2567.33       | 1.000             |
| Tryptophyl-Phasylamin                                                      | 11.4±243.48          | 31.9±504.72          | 1.000             |

Wilcoxon rank-sum test was used on the metabolites. \( P \) value was adjusted using Benjamini-Hochberg false discovery rate (FDR).
| Herbicide          | 2 μg | 5 μg | 10 μg | P<sub>0.05</sub> value |
|-------------------|-----|-----|------|----------------------|
| 1-[(4-Methoxyphenoxy)methyl]-3-pyrazolinone | 865 ± 110 | 1065 ± 130 | 795 ± 120 | 0.005 | 1.000 | 1.000 |
| 1-(Methyl-1H-pyrazol-4-yl)-3-pyrazolinone | 3.7 ± 1.5 | 5.8 ± 1.6 | 7.8 ± 1.8 | 0.006 | 1.000 | 1.000 |
| 1-Hydroxy-2-(3H)-1,2-diphenyl-1,2-oxazole | 5.1 ± 1.4 | 7.8 ± 1.6 | 10.2 ± 2.0 | 0.006 | 1.000 | 1.000 |
| 1-Methyl-2-(3H)-1,2-diphenyl-1,2-oxazole | 523 ± 100 | 657 ± 110 | 877 ± 120 | 0.005 | 1.000 | 1.000 |
| 2-Methyl-3-(4-diethylaminophenyl)-7-oxo-1,2,3,7-tetrahydroquinoline | 18.8 ± 2.5 | 28.6 ± 3.5 | 40.2 ± 4.5 | 0.006 | 1.000 | 1.000 |
| 2-Methyl-4-(4-diethylaminophenyl)-7-oxo-1,2,3,7-tetrahydroquinoline | 2 ± 0.5 | 4 ± 0.8 | 6 ± 1.2 | 0.006 | 1.000 | 1.000 |
| 2-Diphenyl-1,3,4-oxadiazole | 8 ± 1.2 | 12 ± 1.5 | 18 ± 1.8 | 0.006 | 1.000 | 1.000 |
| 2-Diphenyl-1,3,4-thiadiazole | 1.7 ± 0.3 | 2.5 ± 0.5 | 3 ± 0.6 | 0.006 | 1.000 | 1.000 |
| 2-Diphenyl-1,3,4-thiadiazole-5-sulfonamide | 1 ± 0.2 | 1.5 ± 0.3 | 2 ± 0.4 | 0.006 | 1.000 | 1.000 |
| 2-Diphenyl-1,3,4-thiadiazole-5-sulfonamide-3-sulfonic acid | 5 ± 1.2 | 8 ± 1.5 | 10 ± 1.8 | 0.006 | 1.000 | 1.000 |
| 2-Diphenyl-1,3,4-thiadiazole-5-sulfonic acid | 0.5 ± 0.1 | 0.8 ± 0.2 | 1 ± 0.3 | 0.006 | 1.000 | 1.000 |
| 2-Diphenyl-1,3,4-thiadiazole-5-sulfonic acid-3-sulfonic acid | 0.5 ± 0.1 | 0.8 ± 0.2 | 1 ± 0.3 | 0.006 | 1.000 | 1.000 |

Note: The P<sub>0.05</sub> value was adjusted using Bonferroni multiple comparison tests (FDR).
| Parameters                          | B    | SE   | t Stat | df   | P value | OR   | 95% CI (lower-upper) |
|-----------------------------------|------|------|--------|------|---------|------|---------------------|
| Hydromorphone intakes             | 184.92 | 146.07 | 1.234 | 1.000 | 0.999   | 0.000 | 1.000 – 0.000       |
| Urinary Desmethyldihydrocodeine    | 0.080  | 0.080 | 1.000  | 1.000 | 0.209   | 1.083 | 0.927 – 1.226       |
| Clonazepam                        | -4.982 | 1.689 | 2.885  | 1.000 | 0.004   | 0.001 | 0.000 – 0.001       |
| Hydromorphone intakes             | 110.177 | 171.648 | 0.000 | 1.000 | 0.935   | 0.000 | 1.000 – 0.000       |
| Urinary hydromorphone             | 0.022  | 0.011 | 3.567  | 1.000 | 0.064   | 1.023 | 1.000 – 1.047       |
| Clonazepam                        | -7.425 | 1.755 | 4.290  | 1.000 | 0.002   | 0.000 | 0.000 – 0.000       |

*Abbreviations: B, coefficient value; SE, standard error; df, degrees of freedom; OR, 95% confidence interval.*
| Desired   | VIP   |
|----------|------|
| Glutamine| 0.488|
| GABA     | 0.232|
| Glycine  | 0.015|
| Serine   | 0.015|
| Aspartate| 0.015|
| Glutamate| 0.015|
| Alanine  | 0.015|
| Valine   | 0.015|
| Leucine  | 0.015|
| Isoleucine| 0.015|
| Taurine  | 0.015|
| Ornithine| 0.015|
| Arginine | 0.015|
| Proline  | 0.015|
| Histidine| 0.015|
| Glutamine| 0.015|
| Aspartate| 0.015|
| Glutamate| 0.015|
| Alanine  | 0.015|
| Valine   | 0.015|
| Leucine  | 0.015|
| Isoleucine| 0.015|
| Taurine  | 0.015|
| Ornithine| 0.015|
| Arginine | 0.015|
| Proline  | 0.015|
| Histidine| 0.015|
| Glutamine| 0.015|
| Aspartate| 0.015|
| Glutamate| 0.015|
| Alanine  | 0.015|
| Valine   | 0.015|
| Leucine  | 0.015|
| Isoleucine| 0.015|
| Taurine  | 0.015|
| Ornithine| 0.015|
| Arginine | 0.015|
| Proline  | 0.015|
| Histidine| 0.015|
| Glutamine| 0.015|
| Aspartate| 0.015|
| Glutamate| 0.015|
| Alanine  | 0.015|
| Valine   | 0.015|
| Leucine  | 0.015|
| Isoleucine| 0.015|
| Taurine  | 0.015|
| Ornithine| 0.015|
| Arginine | 0.015|
| Proline  | 0.015|
| Histidine| 0.015|
| Glutamine| 0.015|
| Aspartate| 0.015|
| Glutamate| 0.015|
| Alanine  | 0.015|
| Valine   | 0.015|
| Leucine  | 0.015|
| Isoleucine| 0.015|
| Taurine  | 0.015|
| Ornithine| 0.015|
| Arginine | 0.015|
| Proline  | 0.015|
| Histidine| 0.015|
| Glutamine| 0.015|
| Aspartate| 0.015|
| Glutamate| 0.015|
| Alanine  | 0.015|
| Valine   | 0.015|
| Leucine  | 0.015|
| Isoleucine| 0.015|
| Taurine  | 0.015|
| Ornithine| 0.015|
| Arginine | 0.015|
| Proline  | 0.015|
| Histidine| 0.015|
| Glutamine| 0.015|
| Aspartate| 0.015|
| Glutamate| 0.015|
| Alanine  | 0.015|
| Valine   | 0.015|
| Leucine  | 0.015|
| Isoleucine| 0.015|
| Taurine  | 0.015|
| Ornithine| 0.015|
| Arginine | 0.015|
| Proline  | 0.015|
| Histidine| 0.015|
| Glutamine| 0.015|
| Aspartate| 0.015|
| Glutamate| 0.015|
| Alanine  | 0.015|
| Valine   | 0.015|
| Leucine  | 0.015|
| Isoleucine| 0.015|
| Taurine  | 0.015|
| Ornithine| 0.015|
| Arginine | 0.015|
| Proline  | 0.015|
| Histidine| 0.015|
| Glutamine| 0.015|
| Aspartate| 0.015|
| Glutamate| 0.015|
| Alanine  | 0.015|
| Valine   | 0.015|
| Leucine  | 0.015|
| Isoleucine| 0.015|
| Taurine  | 0.015|
| Ornithine| 0.015|
| Arginine | 0.015|
| Proline  | 0.015|
| Histidine| 0.015|
| Glutamine| 0.015|
| Aspartate| 0.015|
| Glutamate| 0.015|
| Alanine  | 0.015|
| Valine   | 0.015|
| Leucine  | 0.015|
| Isoleucine| 0.015|
| Taurine  | 0.015|
| Ornithine| 0.015|
| Arginine | 0.015|
| Proline  | 0.015|
| Histidine| 0.015|
| Glutamine| 0.015|
| Aspartate| 0.015|
| Glutamate| 0.015|
| Alanine  | 0.015|
| Valine   | 0.015|
| Leucine  | 0.015|
| Isoleucine| 0.015|
| Taurine  | 0.015|
| Ornithine| 0.015|
| Arginine | 0.015|
| Proline  | 0.015|
| Histidine| 0.015|
| Glutamine| 0.015|
| Aspartate| 0.015|
| Glutamate| 0.015|
| Alanine  | 0.015|
| Valine   | 0.015|
| Leucine  | 0.015|
| Isoleucine| 0.015|
| Taurine  | 0.015|
| Ornithine| 0.015|
| Arginine | 0.015|
| Proline  | 0.015|
| Histidine| 0.015|
| Glutamine| 0.015|
| Aspartate| 0.015|
| Glutamate| 0.015|
| Alanine  | 0.015|
| Valine   | 0.015|
| Leucine  | 0.015|
| Isoleucine| 0.015|
| Taurine  | 0.015|
| Ornithine| 0.015|
| Arginine | 0.015|
| Proline  | 0.015|
| Histidine| 0.015|
| Glutamine| 0.015|
| Aspartate| 0.015|
| Glutamate| 0.015|
| Alanine  | 0.015|
| Valine   | 0.015|
| Leucine  | 0.015|
| Isoleucine| 0.015|
| Taurine  | 0.015|
| Ornithine| 0.015|
| Arginine | 0.015|
| Proline  | 0.015|
| Histidine| 0.015|
| Metabolite                                                                 | AUC  |
|---------------------------------------------------------------------------|------|
| (-)-Riboflavin                                                           | 0.193|
| 12-Hydroxy-13-C-Δ,g-glucuronide-octadec-4Z-ene                           | 0.044|
| 12-oxo-20-hydroxy-leukotriene B4                                        | 0.015|
| 1-Methylen-3-alpha-androstan-5-alpha-ol-17-one glucuronide               | 0.988|
| 2,3-Dinor-6-keto-prostaglandin F1 a                                      | 0.959|
| 2,3-Dinorbradyne B1                                                       | 0.983|
| 2,6-alpha-hydroxy-19-nortestosterone                                    | 0.467|
| 2-Hydroxy-1,6,6-trimethylcyclohexanone                                   | 0.973|
| 3-(3-oxo-1H-indol-2-ylidene)-1H-indol-2-one                              | 0.307|
| 3-Hydroxy-1-(N-methylbenzoyl)-4H-1-benzopyran-4-one                     | 0.995|
| 3-Methoxybenzeneoxepanic acid                                           | 0.163|
| 4,5-Dihydro-drospirenone-3-sulfate                                      | 0.962|
| 2-(3,5)-Dihydroxypseudo-gamma-valerolactone                             | 0.103|
| 7,8-dihydroxy-1H-chromen-1-one                                          | 0.995|
| Arg-Gly-Asp                                                              | 0.161|
| Aspartic acid                                                            | 0.008|
| Caffeic acid 4-sulfate                                                   | 0.631|
| Cinacalcet C                                                              | 0.952|
| Cinacalcet E                                                             | 0.187|
| cis-1-Renyl pyruvate                                                     | 0.991|
| Cymarin monoglucoside                                                    | 0.471|
| Cys-Val-I-Nal-Met                                                         | 0.987|
| Daidzein 4-O-glucoside                                                   | 0.156|
| Dimethylisobutyl                                                        | 0.347|
| Epsosamol                                                                | 0.184|
| Iturin D8                                                                 | 0.182|
| Marrames A,B,B                                                           | 0.942|
| n-Hydroxybenzoylgeronine                                                 | 0.379|
| Monothioglycolate                                                        | 0.358|
| N-(-Furanyl)glycine                                                      | 0.565|
| N-(1-Methyl-3-oxohexyl)alazine                                          | 0.162|
| Necrostatin, human                                                       | 0.878|
| Nifedipine                                                               | 0.198|
| O-Desacetylmycophenolic acid                                            | 0.186|
| Ocloptadine                                                               | 0.386|
| o-Tyrosine                                                               | 0.173|
| FC(16:0/16:1(9Z))                                                        | 0.452|
| Perilic acid                                                             | 0.964|
| Prostaglandin III                                                        | 0.156|
| Pyrogallol-1-O-sulfate                                                   | 0.304|
| Pyrogallol-2-O-glucuronide                                               | 0.977|
| Pyrogallol-2-O-sulfate                                                   | 0.158|
| Retinyl beta-glucoside                                                   | 0.977|
| Sapoxiolide A                                                            | 0.182|
| Shiokinin                                                                | 0.162|
| Stachydrine                                                              | 0.186|
| Sulfosemazine                                                            | 1.000|
| Tamoxifen                                                                | 0.204|
| TG 46:10, TG(12:3/12:2/19:5)                                             | 0.154|
| Thromboxane B3                                                           | 0.196|
| Triglyceride                                                             | 0.303|
| Tryptophyl-Lysine                                                        | 0.188|
| Tryptophyl-Pheylalanine                                                  | 0.386|

The metabolites displayed in the table are based on area under ROC curve (AUROC). Only the metabolites with AUC ≥ 0.85 are displayed. The 95% confidence interval is calculated using 500 bootstrappings.
| Sequence | Value | Units |
|----------|-------|-------|
| 12345678 | 0.22 | 0.12 |
| 87654321 | 0.22 | 0.12 |
| 98765432 | 0.22 | 0.12 |
| 01234567 | 0.22 | 0.12 |
| 76543210 | 0.22 | 0.12 |
| 65432109 | 0.22 | 0.12 |
| 54321098 | 0.22 | 0.12 |
| 43210987 | 0.22 | 0.12 |
| 32109876 | 0.22 | 0.12 |
| 21098765 | 0.22 | 0.12 |
| 10987654 | 0.22 | 0.12 |

**Note:** The values are presented in a table format, with each sequence shown alongside its corresponding unit.
| Metabolite                          | VIP  |
|------------------------------------|------|
| 1-(Hydroxyimino)acetamide          | 1.07  |
| 1-(2-Hydroxyethyl)imidazole        | 1.05  |
| 1-Histidinol                       | 1.10  |
| 1-Methylimidazole                  | 1.02  |
| 1-Methyl-2-pyridone               | 1.12  |
| 2-Methyl-1,2,4-triazole            | 1.09  |
| 2,2-Dimethyl-1,3-dioxolane         | 1.06  |
| 2,3-Diaminopropionic acid          | 1.10  |
| 2-Aminoimidazole                   | 1.03  |
| 2-Amino-3-methyl-1,2,4-triazole     | 1.13  |
| 2-Amino-4-methyl-1,2,3-thiadiazole | 1.01  |
| 2-Amino-5-methyl-1,2,4-triazole     | 1.06  |
| 2-Aminoisobutyric acid             | 1.12  |
| 2-Amino-2-methylimidazole          | 1.08  |
| 2-Aminopropionic acid              | 1.06  |
| 2-Aminopropanesulfonic acid        | 1.08  |
| 2-Aminosuccinic acid               | 1.12  |
| 2-Amino-2,2-dimethylimidazole      | 1.06  |
| 2-Amino-3,3-dimethyl-1,2,4-triazole| 1.07  |
| 2-Amino-4,4-dimethylimidazole      | 1.08  |
| 2-Amino-5,5-dimethyl-1,2,4-triazole| 1.06  |
| 2-Amino-2,5-dimethyl-1,2,4-triazole| 1.07  |
| 2-Amino-3,5-dimethyl-1,2,4-triazole| 1.08  |
| 2-Amino-4,5-dimethyl-1,2,4-triazole| 1.06  |
| 2-Amino-2,4-dimethylimidazole      | 1.07  |
| 2-Amino-3,4-dimethylimidazole      | 1.08  |
| 2-Amino-4,5-dimethylimidazole      | 1.06  |
| 2-Amino-2,5-dimethyl-1,2,4-triazole| 1.07  |
| 2-Amino-3,4-dimethylimidazole      | 1.08  |
| 2-Amino-4,5-dimethylimidazole      | 1.06  |
| 2-Amino-2,5-dimethyl-1,2,4-triazole| 1.07  |
| 2-Amino-3,4-dimethylimidazole      | 1.08  |
| 2-Amino-4,5-dimethylimidazole      | 1.06  |
| 2-Amino-2,5-dimethyl-1,2,4-triazole| 1.07  |
| 2-Amino-3,4-dimethylimidazole      | 1.08  |
| 2-Amino-4,5-dimethylimidazole      | 1.06  |
| 2-Amino-2,5-dimethyl-1,2,4-triazole| 1.07  |
| 2-Amino-3,4-dimethylimidazole      | 1.08  |
| 2-Amino-4,5-dimethylimidazole      | 1.06  |
| 2-Amino-2,5-dimethyl-1,2,4-triazole| 1.07  |
| 2-Amino-3,4-dimethylimidazole      | 1.08  |
| 2-Amino-4,5-dimethylimidazole      | 1.06  |
| 2-Amino-2,5-dimethyl-1,2,4-triazole| 1.07  |
| 2-Amino-3,4-dimethylimidazole      | 1.08  |
| 2-Amino-4,5-dimethylimidazole      | 1.06  |
| 2-Amino-2,5-dimethyl-1,2,4-triazole| 1.07  |
| 2-Amino-3,4-dimethylimidazole      | 1.08  |
| 2-Amino-4,5-dimethylimidazole      | 1.06  |
| 2-Amino-2,5-dimethyl-1,2,4-triazole| 1.07  |
| 2-Amino-3,4-dimethylimidazole      | 1.08  |
| 2-Amino-4,5-dimethylimidazole      | 1.06  |
| 2-Amino-2,5-dimethyl-1,2,4-triazole| 1.07  |
| 2-Amino-3,4-dimethylimidazole      | 1.08  |
| 2-Amino-4,5-dimethylimidazole      | 1.06  |
| 2-Amino-2,5-dimethyl-1,2,4-triazole| 1.07  |
| 2-Amino-3,4-dimethylimidazole      | 1.08  |
| 2-Amino-4,5-dimethylimidazole      | 1.06  |
| 2-Amino-2,5-dimethyl-1,2,4-triazole| 1.07  |
| 2-Amino-3,4-dimethylimidazole      | 1.08  |
| 2-Amino-4,5-dimethylimidazole      | 1.06  |
| 2-Amino-2,5-dimethyl-1,2,4-triazole| 1.07  |
| 2-Amino-3,4-dimethylimidazole      | 1.08  |
| 2-Amino-4,5-dimethylimidazole      | 1.06  |
| 2-Amino-2,5-dimethyl-1,2,4-triazole| 1.07  |
| 2-Amino-3,4-dimethylimidazole      | 1.08  |
| 2-Amino-4,5-dimethylimidazole      | 1.06  |
| Metabolite                              | AUC   |
|----------------------------------------|-------|
| 11-Hydroxy-12,13-DHODE                 | 0.743 |
| 1-Methylcyclopropenone-2,3-dione-3-oxo | 0.708 |
| 1-Methoxy-4-nitoso-2-butanone           | 0.756 |
| 2,4-Dihydroxy-2,5-dihydroxymethanone   | 0.555 |
| 2-Hydroxy-4-methylbenzonitrile          | 0.625 |
| 2-Acetamidobenzenesulfonic acid        | 0.656 |
| 3-Methoxy-4-nitrobenzoic acid          | 0.569 |
| 4,1-Dihydro-4H-pyran-4-carboxylic acid | 0.589 |
| 4-Hydroxy-2,5-dimethoxybenzene         | 0.587 |
| 4-Hydroxy-3-(4-sulfophenyl)benzoic acid| 0.578 |
| 4-Hydroxy-3-(4-sulfophenyl)benzoic acid| 0.580 |
| 3-Phenylalanine                        | 0.571 |
| Androstenedione glucuronide            | 0.553 |
| Anionic acid                           | 0.693 |
| Caffeic acid 4-sulfate                 | 0.693 |
| Caffeylic acid                         | 0.591 |
| DL-2-Fumaric acid                     | 0.618 |
| Hesperidin                             | 0.572 |
| Hydrosolamic acid                      | 0.654 |
| Isocitrinate B8                        | 0.580 |
| N-N-Methyl-1-carnitine-succinate       | 0.547 |
| Pecanic acid                           | 0.594 |
| Phlorizin                              | 0.661 |
| Progesterone-1-ol-glucuronate          | 0.538 |
| Progesterone-2-ol-glucuronate          | 0.578 |
| Ratapin-2-hydroxyglucuronide           | 0.549 |
| S-Adenosyl-Homocysteine                | 0.571 |
| Scyllo-inositol                        | 0.551 |
| Taurine                                | 0.511 |
| Taurine-1,3-bisulfate                 | 0.511 |
| Triglycerine                           | 0.576 |
| Truxilin-1-lysine                      | 0.622 |

The metabolites displayed in the table are based on area under ROC curve (AUCROC). Only the metabolites with AUC ≥ 0.65 are displayed. The 95% confidence interval is calculated using 500 bootstrappings.
**Tab. S27** Correlation between bacterial genus and cytokines that showed significant difference between controls and SLE

| Genus            | Cytokine | r value | P value | relation |
|------------------|----------|---------|---------|----------|
| Bacteroides      | MIP-1b   | 0.322   | 0.001   | positive |
| Bacteroides      | IP-10    | 0.330   | 0.001   | positive |
| Bacteroides      | IL-12    | -0.339  | 0.001   | negative |
| Bacteroides      | IL-17    | 0.377   | 0.000   | positive |
| Bacteroides      | Entoxin  | 0.426   | 0.000   | positive |
| Gardnerella      | IL-5     | 0.352   | 0.001   | positive |
| Gardnerella      | IL-12    | 0.348   | 0.000   | positive |
| Haemophilus       | IL-13    | 0.317   | 0.002   | positive |
| Haemophilus       | IL-5     | 0.364   | 0.000   | positive |
| Haemophilus       | IL-12    | 0.367   | 0.000   | positive |
| Megamonas        | IP-10    | 0.368   | 0.000   | positive |
| Phocaeicola      | Entoxin  | 0.364   | 0.002   | positive |
| Phocaeicola      | IL-2     | -0.318  | 0.002   | negative |
| Phocaeicola      | IL-8     | 0.327   | 0.001   | positive |
| Phocaeicola      | IL-13    | -0.423  | 0.000   | negative |
| Phocaeicola      | IL-12    | -0.431  | 0.000   | negative |
| Pseudomonas       | MIP-1b   | -0.306  | 0.002   | negative |
| Pseudomonas       | G-CSF    | -0.321  | 0.001   | negative |
| Pseudomonas       | IP-10    | -0.389  | 0.000   | negative |
| Pseudomonas       | IL-8     | -0.512  | 0.000   | negative |
| Rothia           | IL-2     | 0.360   | 0.000   | positive |
| Rothia           | IL-13    | 0.393   | 0.000   | positive |
| Rothia           | IL-5     | 0.449   | 0.000   | positive |
| Rothia           | IL-12    | 0.459   | 0.000   | positive |
| Sphingomonas     | IL-12    | 0.317   | 0.002   | positive |
| Sphingomonas     | IL-8     | -0.356  | 0.000   | negative |
| Staphylococcus   | IL-2     | 0.315   | 0.002   | positive |
| Staphylococcus   | IL-8     | -0.323  | 0.001   | negative |
| Staphylococcus   | IL-12    | 0.375   | 0.000   | positive |
| Staphylococcus   | IP-10    | -0.387  | 0.000   | negative |
| Staphylococcus   | IL-13    | 0.443   | 0.000   | positive |
| Staphylococcus   | IL-5     | 0.457   | 0.000   | positive |
| Streptococcus    | Entoxin  | -0.333  | 0.001   | negative |
| Streptococcus    | IL-13    | 0.358   | 0.000   | positive |
| Streptococcus    | IP-10    | -0.368  | 0.000   | negative |

Spearman correlation evaluated the linear relationship between bacterial genus and cytokine.
| Genus      | Disease Profile | r Value | P Value | Relation |
|------------|-----------------|---------|---------|----------|
| Bacteroides| Uric acid       | 0.428   | 0.002   | positive |
| Haemophilus| Uric acid       | 0.364   | 0.010   | positive |
| Megamonas  | C3              | -0.361  | 0.011   | negative |
| Streptococcus| IgG        | 0.349   | 0.014   | positive |
| Phocaecola | C3              | -0.310  | 0.030   | negative |

Spearman correlation evaluated the linear relationship between bacterial genus and disease profile.