Bioactive Lipid Mediators Profiles In Human Psoriasis Skin And Blood

Alexander V. Sorokin[1], Anthony F. Domenichiello[2], Amit K. Dey[1], Aditya Goyal[1], Shawn M. Rose[3], Martin P. Playford[1], Christopher E. Ramsden[2,4,5] and Nehal N. Mehta[1]

Supplementary Information

SM: Supplementary Methods

SM1

Study population. Participants for the plasma study were middle-aged whites (mean age: psoriasis 48.13 years vs. healthy volunteers 48.37 years) without known history of alcohol use and one case of tobacco smoke. The predominant part of the psoriasis subjects was on topical therapy (66.67%), while 21.67% were receiving systemic therapy. A separate set of subjects enrolled for the skin and serum analyses consisted of middle-aged whites (mean age: psoriasis 56.71 years vs. healthy volunteers 43.29 years) without known history of tobacco or alcohol use. Psoriasis participants had median PASI score of 6.5, consistent with moderate-to-severe psoriasis. Average psoriasis disease duration in this cohort was 23.75 years. The majority of the psoriasis subjects were on topical therapy (62.50%), while 12.50% were receiving biologic therapy. Two psoriasis patients and 2 healthy subjects were on 1000 mg of fish oil per day before enrolling into the study. Two patients had associated psoriatic arthritis (25%). Additionally, high-sensitivity C-reactive protein (hsCRP) level was not significantly different in the psoriasis subjects, compared to healthy (0.76 mg/L vs. 1.30 mg/L, correspondingly, P=0.18).

SM2

LC-MS/MS-based lipidomics of psoriasis skin and serum. Punch biopsies were transferred into FastPrep Lysing Matrix tubes on ice (MP Biomedicals, USA; Lysing Matrix A) and at least 8 times greater volume ice-cold methanol with 0.02% of BHT and 0.02% of EDTA was immediately added to each tube (v/v). Tissue and standard curve were spiked with 9 deuterated internal standards (Cayman Chemical, Ann Arbor, MI, USA). Internal standards were chosen based on their similarity to analytes of interest. A known amount of internal standard was added to each sample and samples were homogenized using a FastPrep-24 homogenizer (MP Bio).

Tissue homogenates were transferred to -80°C for 1 hour to precipitate proteins. Homogenates were centrifuged at 17000g in 4°C for 10 min and supernatant was transferred to a new test tube. Half the supernatant was stored in -80 °C until solid phase extraction (SPE) purification and LC-MS/MS analysis (see below). To permit analysis of total lipid pools the other half of the supernatant was saponified with 2.6% sodium carbonate (by weight) at 60°C for 30 min under gentle shaking. The solution was then neutralized (pH 5-7) using acetic acid and stored in -80°C overnight. Immediately before purification by SPE and LC-MS/MS analysis, lipid extracts (free and saponified total) were added to 9-fold greater volume of ice cold water. Lipids were extracted from 200 µL of plasma by mixing with 500 µL of ice-cold methanol with 0.02% of BHT and 0.02% of EDTA and transferred to -80°C to precipitate proteins (as described above) after addition of known amounts of internal standard. After centrifugation, supernatant was then added to 9-fold greater volume of ice cold water and purified with SPE and analyzed by LC-MS/MS, as described below.

To quantify concentrations of lipid mediators in skin and plasma, lipid extracts were purified using SPE and ran quantified using LC-MS/MS. Briefly, SPE of bioactive lipids from biological matrices was performed using Strata X cartridges (33 u, 200 mg/6 mL, Phenomenex, PA). The cartridges were conditioned with 6 mL of methanol, followed by 6 mL of water before samples were extracted. Samples were washed with 6 mL of 10% methanol. The lipids were eluted with 6 mL of methanol into a glass tube containing 10 µL of 30% glycerol in methanol. The eluate was evaporated to dryness under a stream of nitrogen and reconstituted with 40 µL of methanol, and an aliquot (10 µL) was injected into the LC-MS/MS system. A UPLC (Shimadzu Scientific Instruments, Columbia, MD) coupled with a Qtrap 5500 (AB SCIEX, USA) was used for qualitative and quantitative analysis. Briefly, separation was performed on a ZorBAX RRHD Eclipse Plus C18 column (100 mm x 4 mm; 1.8 µm) (Agilent Corporation, Palo Alto, CA) consisted of (A) 12 mM ammonium acetate solution and acetic acid (100:0.02 v/v) and (B) 12 mM ammonium acetate and was composed of acetonitrile / water / acetic acid (90:10:0.02, v/v/v). The flow rate was 0.5 mL/min. The column oven temperature was set at 30 °C. The elution gradient conditions were as follows: 25-40% B from 0-2.0 min, 40–46% B from 2 to 8 min, 46–57% B from 8 to 9 min, 57–66% B from 9 to 20 min, 66–76% B from 20 to 22 min, 76–100% B from 22 to 27

min, held at 100% B from 27 to 33 min, 100–25% B from 33.1 to 35 min. The mass spectrometer was operated in electrospray negative ionization using scheduled multiple reaction monitoring (sMRM) acquiring MRM data for each analyte with the retention time window of 90s. The source parameters were set as follows: ion spray voltage, −4500 V; nebulizer gas (GS1), 65 psi; turbo-gas (GS2), 70 psi; and the turbo ion spray source temperature (TEM), 500 °C. The analytes were quantified using MRM.

SM3

Sample Preparation. Upon receipt of plasma samples, aliquots were immediately stored at –80 C until time of analysis. Samples were then extracted and prepared for analysis using Metabolon's (Research Triangle Park, NC, USA) standard protocol. Briefly, the sample preparation process was carried out using the automated MicroLab STAR® system from Hamilton Company (Reno, NV, USA). Recovery standards were added prior to the first step in the extraction process for quality control purposes. To remove protein, dissociate small molecules bound to protein or trapped in the precipitated protein matrix, and to recover chemically diverse metabolites, proteins were precipitated with methanol under vigorous shaking for 2 min (Glen Mills GenoGrinder 2000, Clifton, NJ, USA) followed by centrifugation. The resulting extract was divided into two fractions; one for analysis by LC and one for analysis by GC. Samples were placed briefly on a TurboVap® (Zymark / Sotax Corporation, Westborough, MA, USA) to remove the organic solvent. For LC, the samples were stored overnight under nitrogen before preparation for analysis. For GC, each sample was dried under vacuum overnight before preparation for analysis. Samples were then prepared for the appropriate instrument, either LC/MS or GC/MS.

Ultrahigh performance liquid chromatography/Mass Spectrometry (UPLC/MS/MS). The LC/MS portion of the platform was based on a Waters ACQUITY ultra-performance liquid chromatography (UPLC) and a ThermoFisher Scientific Orbitrap Elite high resolution/accurate mass spectrometer, which consisted of a heated electrospray ionization (HESI) source and orbitrap mass analyzer operated at 30,000 mass resolution. The sample extract was dried then reconstituted in acidic or basic LC-compatible solvents, each of which contained 8 or more injection standards at fixed concentrations to ensure injection and chromatographic

consistency. One aliquot was analyzed using acidic positive ion optimized conditions and the other using basic negative ion optimized conditions in two independent injections using separate dedicated columns. Extracts reconstituted in acidic conditions were gradient eluted using water and methanol containing 0.1% formic acid, while the basic extracts, which also used water/methanol, contained 6.5mM ammonium bicarbonate. The MS analysis alternated between MS and data-dependent MS^2 scans using dynamic exclusion.

Gas chromatography/Mass Spectrometry (GC/MS). The samples destined for GC/MS analysis were re-dried under vacuum desiccation for a minimum of 24 hours prior to being derivatized under dried nitrogen using bistrimethyl-silyl-triflouroacetamide (BSTFA). The GC column was 5% phenyl and the temperature ramp is from 40° to 300° C in a 16 minute period. Samples were analyzed on a Thermo-Finnigan Trace DSQ fast-scanning single-quadrupole mass spectrometer using electron impact ionization. The instrument was tuned and calibrated for mass resolution and mass accuracy on a daily basis.

Metabolite identification: Compounds were identified by comparison to library entries of purified standards or recurrent unknown entities. Identification of known chemical entities was based on comparison to metabolomic library entries of more than 2000 commercially available purified standards. The combination of chromatographic properties and mass spectra gave an indication of a match to the specific compound or an isobaric entity. Additional entities could be identified by virtue of their recurrent nature (both chromatographic and mass spectral). These compounds have the potential to be identified by future acquisition of a matching purified standard or by classical structural analysis.

Data normalization. For studies spanning multiple days, a data normalization step was performed to correct variation resulting from instrument inter-day tuning differences. Essentially, each compound was corrected in run-day blocks by registering the medians to equal one (1.00) and normalizing each data point proportionately. For studies that did not require more than one day of analysis, no normalization was necessary, other than for purposes of data visualization.

SM4

Statistical analyses. Data reported as mean ± SEM or median and interquartile range for continuous variables and frequencies (N, %) for categorical variables. For Metabolon data analyses values were normalized in terms of raw area counts. Each biochemical then was rescaled to set the median equal to 1 and described as scaled intensity. For lipid mediator analyses if a particular lipid mediator was below the limit of detection in a sample, its value was imputed as ½ the limit of detection. If a lipid mediator was below the limit of quantitation in more than 50% of the samples in a given group then concentrations of that mediator for that group were not reported. Data were analyzed with a single 2-tailed unpaired Student's *t* test for parametric variables and the Mann-Whitney *t* test for non-parametric variables. The Pearson's Chi-square test was used for categorical variables. For pair-wise Metabolon data comparisons, Welch's t-tests was applied along with the false discovery rate (q-value) adjustment for considering the multiple comparisons. For classification of the best discriminators, Random Forest analysis was used. Linear regression analysis for BMI with different bioactive metabolites and pathway precursors identified in psoriasis plasma was performed using Stata/IC 12.0 (StataCorp LP, College Station, TX, USA). $P \leq 0.05$ was considered statistically significant.

Table S1. Demographic and clinical characteristics of the study groups

Parameter	PSO (N=60)	Healthy (N=30)	P
Demographics and medical history			
Age (years)	48.17 ± 1.64	48.37 ± 2.46	0.47
Male sex, n (%)	30 (50)	15 (50)	1.00
Ethnicity, whites (%)	60 (100)	30 (100)	1.00
Body mass index (kg/m^2)	30.76 ± 0.99	27.32 ± 1.12	**0.02**
Type 2 diabetes mellitus, n (%)	0 (0)	0 (0)	-
Current tobacco use, n (%)	1 (1.7)	0 (0)	0.51
Current alcohol use, n (%)	0 (0)	0 (0)	-
Clinical and laboratory values			
Systolic blood pressure (mmHg)	127.9 ± 2.83		
Diastolic blood pressure (mmHg)	80.51 ± 2.16		
Total cholesterol (mg/dl)	189.5 ± 5.30	162.08 ± 8.16	**0.002**
Triglycerides (mg/dl)	146 ± 13.94		
HDL cholesterol (mg/dl)	55.5 ± 2.82		
LDL cholesterol (mg/dl)	109.4 ± 4.47		
ApoA1 (mg/L)	161.2 ± 5.24		
ApoB (mg/L)	99.2 ± 3.21		
ApoB / ApoA1	0.66 ± 0.32		
Glucose (mg/dl)	89.45 ± 1.71		
Psoriasis Treatment			
Topical therapy, n (%)	40 (66.67)		
Biologic therapy, n (%)	0 (0)		
Systemic therapy, n (%)	13 (21.67)		

HDL, high-density lipoprotein; LDL, low-density lipoprotein. Data represented as mean ± SE and as n (%) for categorical variables.

Table S2. Demographic and clinical characteristics of the separate study groups

Parameter	PSO (N=8)	Healthy (N=7)	P
Demographics and medical history			
Age (years)	56.71 ± 5.63	43.29 ± 5.92	0.06
Male sex, n (%)	6 (75)	6 (85)	0.61
Ethnicity, whites (%)	8 (100)	7 (100)	1.00
Body mass index (kg/m^2)	32.43 ± 2.61	27.36 ± 1.98	0.08
Hypertension, n (%)	2 (25)	2 (29)	0.88
Hyperlipidemia, n (%)	5 (63)	4 (57)	0.83
Type 2 diabetes mellitus, n (%)	1 (13)	1 (14)	0.92
Current tobacco use, n (%)	0 (0)	0 (0)	-
Current alcohol use, n (%)	0 (0)	0 (0)	-
Clinical and laboratory values			
Systolic blood pressure (mmHg)	122.6 ± 5.79	111.7 ± 4.37	0.08
Diastolic blood pressure (mmHg)	72.6 ± 2.63	67.9 ± 3.60	0.15
Total cholesterol (mg/dl)	160.8 ± 9.06	178.4 ± 19.47	0.20
Triglycerides (mg/dl)	120 ± 20.32	103.6 ± 22.28	0.30
HDL cholesterol (mg/dl)	52.5 ± 6.08	54.6 ± 5.62	0.40
LDL cholesterol (mg/dl)	84.3 ± 6.53	103.3 ± 20.50	0.18
ApoA1 (mg/L)	149.4 ± 7.87	142.9 ± 6.90	0.27
ApoB (mg/L)	78.6 ± 5.13	84.4 ± 10.57	0.31
ApoB / ApoA1	0.64 ± 0.13	0.60 ± 0.08	0.40
FRS (IQR)	2.5 (1-8.5)	6 (1-7)	0.86
hsCRP (mg/L) (IQR)	0.76 (0.55-1.37)	1.30 (1.00-3.8)	0.18
Glucose (mg/dl)	94.25 ± 4.45	96.00 ± 4.87	0.40
Insulin (mg/dl)	15.28 ± 4.12	15.64 ± 5.43	0.48
WBC (cells/L)	6.51 ± 0.60	7.38 ± 0.68	0.18
Psoriasis Severity and Treatment			
Disease duration (years)	23.75 ± 5.88		
PASI score (IQR)	6.5 (5.4-14.8)		
Psoriatic arthritis, n (%)	2 (25)		
Topical therapy, n (%)	5 (62.50)		
Biologic therapy, n (%)	1 (12.50)		
Systemic therapy, n (%)	0 (0)		

FRS, Framingham Risk Score; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; PASI, psoriasis area and severity index; PSO, psoriasis; WBC, white blood cell. Data are mean ± SE or median (Interquartile Range) for parametric and non-parametric variables respectively and as n (%) for categorical variables. P values were derived from a single unpaired 2-tailed t test for parametric variables and the Mann-Whitney test for non-parametric variables. The Pearson's Chi-square test was used for categorical variables. $P<0.05$ was considered statistically significant.

Table S3. Free form of bioactive SPM and pathway precursors identified in psoriasis and healthy skin

Bioactive LM / Pathway Precursors	**Lipid mediator levels (ng/g)**					
AA Metabolome	**Lesional Skin**	**Non-Lesional Skin**	***P**	**Healthy**	**†P**	**#P**
LXA4	*	*	–	*	–	–
LXB4	*	*	–	*	–	–
5,6-EET	*	*	–	*	–	–
8,9-EET	3.8 (1.0-11.3)	*	–	*	–	–
11,12-EET	0.8 (0.6-3.2)	2.2 (1.5-7.5)	0.46	*	–	–
14,15-EET	0.5 (0.3-2.2)	1.1 (0.6-4.3)	0.14	*	–	–
5-oxoETE	*	*	–	*	–	–
LTB4	*	*	–	*	–	–
PGE2	108.1 (16.0-345.4)	*	–	*	–	–
PGD2	–	–	–	–	–	–
PGF2α	*	*	–	*	–	–
8-IsoPGF2a	4.5 (0.3-11.8)	5.2 (4.3-14.4)	0.92	6.7 (0.5-21.7)	0.36	0.46
TXB2	1.5 (0.7-7.0)	3.5 (2.3-9.0)	**0.01**	1.9 (1.1-3.6)	0.42	0.40
20-HETE	*	*	–	*	–	–
15-HETE	31.1 (12.3-323.4)	71.7 (18.0-1224.9)	0.34	3.1 (1.4-5.3)	**0.02**	**0.04**
12-HETE	395.0 (135.4-2351.6)	155.8 (29.3-206.4)	**0.05**	3.1 (1.8-16.7)	**0.004**	**0.03**
11-HETE	13.9 (1.0-44.3)	1.8 (1.0-27.6)	0.08	0.9 (0.7-1.3)	**0.05**	0.16
9-HETE	*	7.6 (5.0-30.2)	0.06	4.0 (3.0-5.1)	**0.03**	-
8-HETE	*	6.8 (4.8-29.1)	0.09	3.8 (2.9-4.8)	**0.005**	-
5-HETE	5.2 (1.2-14.2)	2.9 (1.2-14.8)	**0.05**	1.2 (1.0-1.6)	0.17	0.17
LA Metabolome						
9-HODE	307.8 (31.5-606.1)	12.0 (7.4-108.3)	**0.005**	5.6 (4.6-7.1)	**0.002**	**0.04**
13-HODE	607.9 (56.9-1523.7)	36.4 (14.8-1222.3)	**0.02**	5.4 (4.4-10.9)	**0.001**	**0.05**
9,10-EpOME	3.3 (1.2-5.8)	0.8 (0.5-5.6)	**0.05**	0.4 (0.2-0.5)	**0.02**	**0.05**
12,13-EpOME	*	*	–	*	–	–
9,10-DiHOME	3.6 (1.5-5.6)	1.0 (0.8-3.8)	0.07	1.3 (0.9-2.5)	0.17	0.73
12,13-DiHOME	3.9 (2.1-6.5)	1.7 (1.3-6.7)	**0.05**	2.1 (1.4-2.8)	0.11	1.00
9-oxoODE	194.0 (28.9-376.2)	0.3 (0.2-14.1)	**0.003**	0.2 (0.1-0.2)	**0.001**	**0.06**
13-oxoODE	528.4 (66.9-1100.2)	10.8 (6.4-172.9)	**0.003**	5.8 (4.9-6.3)	**0.001**	**0.04**
ALA Metabolome						
9-HOTrE	0.4 (0.1-1.1)	0.2 (0.1-0.6)	0.12	0.04 (0.03-0.1)	**0.01**	**0.004**
13-HOTrE	10.5 (3.0-22.8)	*	–	*	–	–
DHA Metabolome						
RvD1	*	*	–	*	–	–
RvD2	*	*	–	*	–	–
Mar1	*	*	–	*	–	–
16,17-EDP	*	*	–	*	–	–
19(20)-EDP	*	*	–	*	–	–

10S,17S-diHDHA	*	*	–	*	–	–
17-HDHA	41.5 (10.7-193.5)	25.6 (7.7-578.2)	0.29	*	–	–
14-HDHA	17.6 (7.5-38.0)	7.3 (2.3-26.4)	0.37	*	–	–
7-HDHA	11.5 (5.6-25.8)	*	–	*	–	–
4-HDHA	*	*	–	*	–	–
EPA Metabolome						–
18-HEPE	*	*	–	*	–	–
17(18)-EpETE	*	*	–	*	–	–
14(15)-EpETE	*	*	–	*	–	–

Quantification of bioactive lipid mediators (LM) and pathway precursors were assessed by liquid chromatography tandem mass spectrometry–based (LC-MS/MS–based) metabololipidomics. Results are expressed as ng/g tissue. Detection limit was approximately 0.02 ng/sample; * denotes below limits. Results represented as standardized beta coefficient from 7–8 subjects per group. *P compared between lesional vs. non-lesional skin. †P compared between lesional vs. healthy skin. Data are median (Interquartile Range) for non-parametric variables. $^{\#}$P compared between non-lesional vs. healthy skin. P values were derived from Mann-Whitney test for non-parametric variables. $P<0.05$ was considered statistically significant.

Table S4. Total form of bioactive SPM and pathway precursors identified in psoriasis and healthy skin

Bioactive LM / Pathway Precursors	**Lipid mediator levels (ng/g)**					
AA Metabolome	**Lesional Skin**	**Non-Lesional Skin**	***P**	**Healthy**	**†P**	**#P**
LXA4	*	*	–	*	–	–
LXB4	*	*	–	*	–	–
5,6-EET	422.6 (6.1-985.9)	145.0 (82.6-515.8)	0.46	93.2 (10.4-647.2)	1.00	0.62
8.9-EET	46.7 (26.5-62.3)	56.9 (19.7-790.2)	0.92	21.0 (8.9-279.5)	0.56	0.42
11,12-EET	43.4 (23.6-59.8)	44.3 (19.7-115.6)	0.21	23.5 (10.2-36.7)	0.20	0.36
14,15-EET	33.5 (16.8-57.8)	33.7 (19.4-90.6)	0.17	19.2 (9.5-27.8)	0.16	0.25
5-oxoETE	1129.5 (808.4-1582.4)	1086.4 (755.8-2675.8)	0.25	731.6 (663.9-1470.6)	0.35	0.30
LTB4	*	*	–	*	–	–
PGE2	–	–	–	–	–	–
PGD2	–	–	–	–	–	–
PGF2α	–	–	–	–	–	–
8-IsoPGF2a	–	–	–	–	–	–
TXB2	*	*	–	*	–	–
20-HETE	*	*	–	*	–	–
15-HETE	125.8 (47.0-458.4)	225.5 (99.9-2371.8)	0.75	48.4 (38.2-99.3)	0.11	0.11
12-HETE	550.0 (199.9-2475.2)	253.3 (65.0-2226.4)	**0.03**	51.7 (18.5-93.1)	**0.02**	0.08
11-HETE	36.5 (21.1-85.1)	24.4 (17.8-136.4)	0.09	13.1 (8.3-17.8)	0.06	0.08
9-HETE	46.8 (26.8-113.5)	42.9 (29.3-269.0)	0.19	21.2 (18.9-25.5)	**0.05**	0.06
8-HETE	73.5 (22.0-153.5)	23.9 (16.9-193.9)	**0.02**	12.9 (8.1-15.5)	**0.04**	0.11
5-HETE	62.3 (44.2-115.8)	77.8 (45.5-398.8)	0.06	70.0 (44.1-94.0)	0.91	0.64
LA Metabolome						
9-HODE	553.1 (121.0-858.2)	161.1 (133.5-960.9)	**0.02**	126.2 (94.4-134.8)	0.13	0.06
13-HODE	904.6 (154.9-1879.5)	209.2 (183.4-2297.9)	**0.05**	150.0 (101.5-154.0)	**0.05**	**0.02**
Total HODE						
9,10-EpOME	77.1 (38.7-102.0)	107.7 (66.3-562.2)	0.83	52.8 (28.5-104.1)	0.73	0.13
12,13-EpOME	177.2 (88.1-252.5)	244.7 (148.6-1409.2)	0.91	120.0 (65.5-241.3)	0.73	0.06
9,10-DiHOME	5.6 (4.5-11.2)	5.5 (3.5-12.7)	0.21	3.4 (2.3-5.6)	0.13	0.25

12,13-DiHOME	13.0 (7.8-20.2)	12.9 (7.3-29.5)	0.21	8.8 (4.6-15.6)	0.35	0.36
9-oxoODE	383.8 (163.1-662.8)	224.3 (165.1-798.7)	**0.01**	120.4 (90.9-252.6)	0.11	0.25
13-oxoODE	618.3 (165.6-1163.2)	236.4 (170.9-993.8)	**0.02**	131.5 (89.2-264.7)	0.08	0.20
ALA Metabolome						
9-HOTrE	1.2 (0.7-2.8)	1.2 (0.9-3.5)	0.40	0.9 (0.6-1.0)	0.49	0.08
13-HOTrE	15.1 (9.5-31.5)	15.2 (11.5-83.0)	0.86	16.0 (10.1-17.1)	0.56	0.95
DHA Metabolome						
RvD1	*	*	–	*	–	–
RvD2	*	*	–	*	–	–
Mar1	*	*	–	*	–	–
16,17-EDP	12.5 (7.6-28.3)	19.8 (9.9-56.5)	0.49	–	–	–
19(20)-EDP	13.1 (8.3-31.2)	16.4 (10.7-57.7)	0.35	10.1 (4.5-16.8)	0.35	0.20
10S,17S-diHDHA	*	*	–	*	–	–
17-HDHA	98.7 (36.7-338.0)	93.3 (52.6-861.4)	0.30	48.1 (14.1-59.0)	0.20	0.09
14-HDHA	40.8 (13.8-60.8)	22.0 (8.6-136.3)	0.16	5.4 (4.4-9.6)	**0.03**	**0.05**
7-HDHA	20.6 (8.9-27.4)	14.5 (4.5-53.8)	0.09	*	–	–
4-HDHA	21.6 (18.3-63.3)	27.7 (17.0-127.9)	0.06	17.8 (13.6-29.5)	0.25	0.30
EPA Metabolome						
18-HEPE	1.9 (1.3-7.0)	3.3 (2.2-20.1)	0.41	2.9 (1.5-3.2)	1.00	0.09
17(18)-EpETE	*	*	–	*	–	–
14(15)-EpETE	0.7 (0.2-1.5)	2.1 (0.6-7.0)	0.38	*	–	–

Quantification of bioactive lipid mediators (LM) and pathway precursors were assessed by liquid chromatography tandem mass spectrometry–based (LC-MS/MS–based) metabololipidomics. Results are expressed as ng/g tissue. Detection limit was approximately 0.03 ng/sample; * denotes below limits. Results represented as standardized beta coefficient from 7–8 subjects per group. *P compared between lesional vs. non-lesional skin. †P compared between lesional vs. healthy skin. Data are median (Interquartile Range) for non-parametric variables. $^{\#}$P compared between non-lesional vs. healthy skin. P values were derived from Mann-Whitney test for non-parametric variables. $P<0.05$ was considered statistically significant.

Table S5. Bioactive SPM and pathway precursors identified in psoriasis and healthy serum

Bioactive LM / Pathway Precursors			
AA Metabolome	**Psoriasis**	**Healthy**	**P**
LXA4	*	*	–
LXB4	*	*	–
5,6-EET	*	*	–
8.9-EET	0.11 (0.09, 0.12)	0.14 (0.11, 0.34)	0.18
11,12-EET	0.08 (0.07, 0.09)	0.11 (0.07, 0.13)	0.30
14,15-EET	0.14 (0.14, 0.17)	0.20 (0.15, 0.24)	**0.05**
5-oxoETE	0.10 (0.09, 0.13)	0.13 (0.10, 0.17)	0.37
LTB4	0.23 (0.15, 0.28)	0.41 (0.27, 0.45)	0.12
PGE2	0.09 (0.06, 0.14)	0.11 (0.06, 0.20)	0.52
PGD2	*	*	–
PGF2α	*	*	–
8-IsoPGF2a	*	*	–
TXB2	0.97 (0.17, 10.04)	12.86 (0.41, 31.40)	0.25
20-HETE	0.63 (0.39, 0.77)	0.89 (0.74, 1.15)	0.07
15-HETE	0.50 (0.31, 0.80)	1.44 (1.12, 3.25)	**0.02**
12-HETE	14.85 (4.70, 30.20)	74.25 (37.40, 524.00)	**0.04**
11-HETE	0.20 (0.18, 0.69)	0.99 (0.60, 1.59)	**0.04**
9-HETE	0.25 (0.14, 0.25)	0.24 (0.14, 0.25)	0.80
8-HETE	0.25 (0.21, 0.29)	0.33 (0.25, 1.28)	0.07
5-HETE	0.80 (0.69, 1.63)	1.31 (1.09, 1.45)	0.61
LA Metabolome			
9-HODE	2.96 (2.10, 3.22)	3.60 (2.80, 4.26)	0.12
13-HODE	3.00 (2.22, 3.43)	4.91 (2.41, 7.21)	0.30
9,10-EpOME	0.97 (0.84, 1.11)	1.23 (0.70, 2.07)	0.44
12,13-EpOME	4.28 (3.49, 5.06)	5.21 (2.94, 6.99)	0.80
9,10-DiHOME	1.10 (0.72, 1.43)	0.93 (0.75, 1.00)	0.61
12,13-DiHOME	1.14 (0.85, 2.05)	1.21 (0.82, 1.85)	0.90
9-oxoODE	0.37 (0.34, 0.50)	0.44 (0.25, 0.47)	0.90
13-oxoODE	0.65 (0.52, 0.75)	0.71 (0.57, 0.80)	0.90
ALA Metabolome			
9-HOTrE	0.13 (0.10, 0.17)	0.13 (0.11, 0.19)	0.52
13-HOTrE	0.18 (0.15, 0.36)	0.33 (0.21, 0.46)	**0.05**
DHA Metabolome			
RvD1	–	–	–
RvD2	0.06 (0.04, 0.08)	*	–
Mar1	*	*	–
16,17-EDP	0.11 (0.09, 0.16)	0.13 (0.11, 0.14)	0.95
19(20)-EDP	0.20 (0.13, 0.27)	0.24 (0.19, 0.28)	0.44
10S,17S-diHDHA	–	–	–
17-HDHA	0.49 (0.36, 0.59)	1.13 (0.53, 3.09)	0.09
14-HDHA	2.76 (1.15, 5.40)	19.56 (3.03, 71.40)	0.07
7-HDHA	0.04 (0.01, 0.05)	0.08 (0.03, 0.13)	0.14
4-HDHA	0.20 (0.14, 0.40)	0.20 (0.17, 0.26)	0.95

EPA Metabolome			
18-HEPE	0.15 (0.11, 0.18)	0.15 (0.14, 0.29)	0.52
17(18)-EpETE	*	*	–
14(15)-EpETE	0.01 (0.01, 0.02)	*	–

Quantification of bioactive lipid mediators (LM) and pathway precursors were assessed by liquid chromatography tandem mass spectrometry–based (LC-MS/MS–based) metabololipidomics. Results are expressed as ng/ml. Detection limit was approximately 0.02 ng; – denotes below limits; * denotes only detection in one subject. Values are reported in the table as median (Interquartile Range) for non-parametric variables from 7–8 subjects per group. P values were derived from Mann-Whitney test for non-parametric variables. $P<0.05$ was considered statistically significant.

Table S6. Complete metabolomic profiling of psoriasis and healthy plasma

Pathway	Biochemical Name	Fold Change		All Samples		Omit Outlier	
		All Samples	Omit Outlier	p	q	p	q
Glycine, serine and threonine metabolism	glycine	0.87	0.88	0.0341	0.0919	0.0506	0.1158
	sarcosine (N-Methylglycine)	1.33	1.32	0.0614	0.1309	0.0815	0.1582
	dimethylglycine	1.06	1.06	0.8224	0.6062	0.8432	0.6068
	N-acetylglycine	1.21	1.21	0.4995	0.4804	0.5046	0.4762
	serine	0.82	0.83	0.0116	0.0397	0.0174	0.0557
	N-acetylserine	1.09	1.09	0.0767	0.1504	0.0820	0.1583
	threonine	0.89	0.89	0.0020	0.0127	0.0015	0.0109
	N-acetylthreonine	0.99	0.99	0.9589	0.6365	0.9785	0.6394
	betaine	0.89	0.90	0.0437	0.1068	0.0557	0.1210
Alanine and aspartate metabolism	aspartate	0.89	0.89	0.1349	0.2173	0.1377	0.2204
	asparagine	0.68	0.69	0.0046	0.0206	0.0069	0.0287
	beta-alanine	0.85	0.85	0.1044	0.1812	0.1086	0.1935
	3-ureidopropionate	1.11	1.10	0.5704	0.5120	0.6512	0.5390
	N-acetyl-beta-alanine	1.07	1.07	0.1606	0.2435	0.1775	0.2540
	alanine	0.85	0.85	0.0019	0.0121	0.0026	0.0149
	N-acetylalanine	1.05	1.05	0.1621	0.2446	0.1718	0.2494
Glutamate metabolism	glutamate	1.49	1.41	0.0015	0.0102	0.0025	0.0149
	glutamine	0.97	0.99	0.2345	0.3060	0.4995	0.4746
	pyroglutamin	1.14	1.15	0.7260	0.5761	0.6950	0.5436
	N-acetyl-aspartyl-glutamate (NAAG)	1.13	1.13	0.0414	0.1034	0.0410	0.1031
	N-acetylglutamine	0.90	0.88	0.0799	0.1532	0.0595	0.1277
Histidine metabolism	histidine	0.95	0.95	0.2999	0.3553	0.3303	0.3681
	N-acetylhistidine	0.96	0.93	0.8743	0.6190	0.9494	0.6342
	trans-urocanate	0.81	0.82	0.1595	0.2435	0.2082	0.2841
	3-methylhistidine	1.04	1.04	0.8752	0.6190	0.9054	0.6265
	N-acetyl-3-methylhistidine	1.12	1.07	0.8755	0.6190	0.9537	0.6357
	1-methylhistidine	0.95	0.94	0.7229	0.5761	0.6047	0.5206
	imidazole lactate	1.08	1.06	0.5686	0.5120	0.7027	0.5454
	1-methylimidazoleacetate	1.44	1.40	0.0107	0.0374	0.0143	0.0485
	imidazole propionate	0.95	0.94	0.5168	0.4862	0.4653	0.4593
	N-acetyl-1-methylhistidine	0.98	0.94	0.7267	0.5761	0.6037	0.5206
Lysine metabolism	lysine	0.90	0.89	0.0205	0.0625	0.0116	0.0399
	2-aminoadipate	1.30	1.30	0.0025	0.0140	0.0024	0.0145
	pipecolate	0.88	0.88	0.1689	0.2528	0.1576	0.2389
	N-6-trimethyllysine	1.09	1.09	0.5744	0.5126	0.6060	0.5206
	N6-acetyllysine	0.96	0.95	0.3168	0.3607	0.2178	0.2934
	glutarylcarnitine (C5)	0.91	0.89	0.6955	0.5692	0.5666	0.5084
Phenylalanine & tyrosine metabolism	phenyllactate (PLA)	0.94	0.88	0.3210	0.3607	0.1779	0.2540
	phenylalanine	0.94	0.94	0.0941	0.1711	0.0778	0.1552
	p-cresol sulfate	0.94	0.94	0.6535	0.5466	0.6167	0.5260
	o-cresol sulfate	0.85	0.86	0.0145	0.0466	0.0163	0.0525

	phenylpyruvate	0.92	0.92	0.1718	0.2560	0.1706	0.2494
	gentisate	1.00	1.00				
	tyrosine	0.97	0.97	0.6256	0.5326	0.5533	0.5003
	3-(4-hydroxyphenyl)lactate	1.02	0.99	0.8095	0.6005	0.9869	0.6407
	vanillylmandelate (VMA)	1.09	1.10	0.5460	0.5041	0.4781	0.4639
	4-hydroxyphenylacetate	0.69	**0.66**	0.1131	0.1905	0.0792	0.1563
	3-methoxytyrosine	**1.13**	**1.14**	0.0660	0.1320	0.0537	0.1182
	N-acetylphenylalanine	1.07	0.98	0.7456	0.5791	0.9914	0.6425
	N-acetyltyrosine	0.98	0.94	0.5600	0.5080	0.4001	0.4202
	phenylacetylglutamine	0.80	**0.80**	0.1113	0.1903	0.0956	0.1782
	3-(3-hydroxyphenyl)propionate	0.69	0.68	0.7036	0.5721	0.6570	0.5390
	3-phenylpropionate (hydrocinnamate)	0.58	0.59	0.1208	0.1978	0.1448	0.2274
	phenol sulfate	1.24	1.25	0.2773	0.3426	0.1917	0.2653
	3-[3-(sulfooxy)phenyl]propanoic acid	0.81	0.81	0.6865	0.5647	0.6723	0.5400
Tryptophan metabolism	xanthurenate	**0.82**	0.83	0.0869	0.1632	0.1066	0.1927
	kynurenate	1.01	1.01	0.8629	0.6190	0.8857	0.6168
	kynurenine	**1.13**	**1.13**	0.0371	0.0975	0.0412	0.1031
	tryptophan	0.99	0.99	0.7373	0.5778	0.6387	0.5351
	indolelactate	0.96	0.88	0.3611	0.3893	0.1776	0.2540
	indoleacetate	**0.90**	**0.90**	0.0996	0.1762	0.0894	0.1688
	indolebutyrate	0.76	0.76	0.4605	0.4568	0.5105	0.4778
	tryptophan betaine	1.00	1.01	0.1399	0.2217	0.1265	0.2111
	serotonin (5HT)	**3.94**	**3.99**	0.0000	0.0000	0.0000	0.0000
	N-acetyltryptophan	1.05	0.96	0.9578	0.6365	0.7580	0.5740
	C-glycosyltryptophan	**1.12**	**1.12**	0.0145	0.0466	0.0160	0.0520
	5-hydroxyindoleacetate	0.65	0.64	0.2738	0.3395	0.2615	0.3248
	methyl indole-3-acetate	1.17	1.17	0.2383	0.3077	0.2194	0.2934
	3-indoxyl sulfate	0.94	0.94	0.5037	0.4804	0.5015	0.4746
	indolepropionate	0.76	0.76	0.1600	0.2435	0.1645	0.2447
	indoleacetylglutamine	0.88	0.88	0.3640	0.3912	0.3475	0.3791
Valine, leucine and isoleucine metabolism	3-methyl-2-oxobutyrate	1.00	1.00	0.9402	0.6314	0.9331	0.6307
	3-methyl-2-oxovalerate	0.97	0.95	0.7798	0.5879	0.6145	0.5253
	levulinate (4-oxovalerate)	**0.73**	**0.73**	0.0695	0.1378	0.0758	0.1522
	beta-hydroxyisovalerate	1.04	1.04	0.4165	0.4221	0.4226	0.4335
	alpha-hydroxyisocaproate	1.04	0.99	0.8453	0.6152	0.6405	0.5351
	isoleucine	0.95	0.95	0.2942	0.3534	0.2226	0.2935
	leucine	0.93	0.92	0.1419	0.2239	0.1140	0.1978
	N-acetylleucine	**0.91**	**0.87**	0.0571	0.1246	0.0220	0.0663
	N-acetylvaline	0.99	0.98	0.9989	0.6494	0.8779	0.6151
	N-acetylisoleucine	1.00	0.96	0.7283	0.5761	0.5174	0.4804
	tigloylglycine	0.77	0.78	0.1000	0.1762	0.1049	0.1908
	valine	1.00	1.00	0.9707	0.6415	0.9843	0.6407
	3-hydroxyisobutyrate	0.91	0.91	0.3056	0.3588	0.2829	0.3381
	4-methyl-2-oxopentanoate	0.97	0.95	0.7271	0.5761	0.6260	0.5300
	3-hydroxy-2-ethylpropionate	**1.18**	**1.19**	0.0551	0.1210	0.0547	0.1196

	alpha-hydroxyisovalerate	1.19	1.11	0.2727	0.3395	0.3834	0.4049
	isovalerylglycine	**0.49**	**0.49**	0.0006	0.0053	0.0005	0.0046
	isobutyrylcarnitine	**0.70**	**0.70**	0.0076	0.0303	0.0076	0.0310
	2-hydroxy-3-methylvalerate	1.04	0.97	0.9649	0.6393	0.7508	0.5712
	2-methylbutyrylcarnitine (C5)	0.97	0.96	0.9394	0.6314	0.8835	0.6165
	isovalerylcarnitine	**0.67**	**0.67**	0.0096	0.0348	0.0089	0.0334
	hydroxyisovaleroyl carnitine	0.97	0.96	0.5430	0.5027	0.4970	0.4746
	tiglyl carnitine	0.94	0.93	0.3844	0.4048	0.3344	0.3702
	3-methylglutarylcarnitine (C6)	0.94	0.94	0.7515	0.5816	0.7814	0.5880
Cysteine, methionine, SAM, taurine metabolism	cysteine	**0.89**	**0.89**	0.0373	0.0975	0.0339	0.0914
	S-methylcysteine	1.08	1.09	0.5558	0.5080	0.5103	0.4778
	N-formylmethionine	0.99	0.99	0.8996	0.6221	0.9367	0.6307
	taurine	1.04	1.05	0.5637	0.5097	0.5667	0.5084
	S-adenosylhomocysteine (SAH)	**0.90**	**0.89**	0.0604	0.1302	0.0393	0.1005
	methionine	**0.86**	**0.85**	0.0026	0.0146	0.0017	0.0119
	N-acetylmethionine	**0.76**	**0.76**	0.0192	0.0592	0.0250	0.0720
	alpha-ketobutyrate	**1.31**	**1.31**	0.0400	0.1022	0.0447	0.1079
	2-hydroxybutyrate (AHB)	**1.25**	1.19	0.0776	0.1507	0.1120	0.1954
	4-amino-2-hydroxybutyate	**0.86**	**0.87**	0.0267	0.0764	0.0379	0.0977
Urea cycle; arginine-, proline-, metabolism	dimethylarginine (SDMA + ADMA)	0.98	0.99	0.6102	0.5262	0.5843	0.5163
	arginine	**1.21**	**1.20**	0.0630	0.1314	0.0713	0.1454
	homoarginine	0.94	0.92	0.3905	0.4054	0.3082	0.3537
	N-acetylarginine	0.83	0.82	0.1746	0.2574	0.1503	0.2338
	ornithine	**0.63**	**0.62**	0.0000	0.0002	0.0000	0.0002
	urea	0.93	0.93	0.2207	0.2918	0.2334	0.3008
	proline	0.94	0.94	0.2044	0.2817	0.1797	0.2544
	citrulline	0.96	0.95	0.4509	0.4511	0.3763	0.3987
	N-methyl proline	0.82	0.79	0.2818	0.3445	0.2349	0.3017
	trans-4-hydroxyproline	**0.82**	**0.82**	0.0419	0.1040	0.0496	0.1148
	homocitrulline	0.87	0.83	0.3542	0.3842	0.2609	0.3248
	N-delta-acetylornithine	0.91	0.91	0.7136	0.5761	0.6934	0.5436
	N2,N5-diacetylornithine	0.90	0.88	0.3760	0.3992	0.3016	0.3517
Creatine metabolism	creatine	0.90	0.89	0.6057	0.5244	0.5451	0.4955
	creatinine	1.02	1.01	0.7736	0.5864	0.8570	0.6116
Butanoate metabolism	2-aminobutyrate	1.08	1.08	0.2698	0.3394	0.2691	0.3296
Polyamine metabolism	5-methylthioadenosine (MTA)	0.95	0.94	0.1757	0.2574	0.1442	0.2274
	acisoga	**1.18**	**1.19**	0.0794	0.1531	0.0678	0.1410
Guanidino and acetamido metabolism	4-guanidinobutanoate	**0.76**	**0.75**	0.0062	0.0258	0.0044	0.0210
	4-acetamidobutanoate	0.96	0.96	0.7763	0.5872	0.6850	0.5436
Glutathione metabolism	5-oxoproline	**0.86**	**0.86**	0.0271	0.0764	0.0286	0.0804
	cysteine-glutathione disulfide	**0.56**	**0.57**	0.0012	0.0086	0.0015	0.0109
Dipeptide	glycylvaline	1.00	1.00				
	glycylleucine	**0.80**	**0.80**	0.0994	0.1762	0.0989	0.1817
	asparagylleucine	1.16	1.14	0.3370	0.3726	0.4043	0.4232
	isoleucylaspartate	1.07	1.07	0.1799	0.2609	0.1608	0.2404

	isoleucylisoleucine	1.08	1.08	0.4310	0.4350	0.4585	0.4564
	isoleucylleucine	**1.18**	**1.18**	0.0223	0.0659	0.0221	0.0663
	leucylleucine	**4.78**	**4.60**	0.0000	0.0000	0.0000	0.0000
	pro-hydroxy-pro	0.99	0.99	0.9031	0.6230	0.9354	0.6307
	phenylalanylphenylalanine	0.10	0.10	0.6443	0.5416	0.6327	0.5343
	phenylalanylalanine	1.16	1.15	0.2892	0.3486	0.3321	0.3688
	phenylalanylvaline	0.91	0.91	0.9963	0.6494	0.9996	0.6466
	phenylalanylglycine	**0.72**	**0.72**	0.0612	0.1309	0.0708	0.1454
	phenylalanylmethionine	1.01	1.02	0.9212	0.6285	0.8244	0.6046
	pyroglutamylglutamine	1.03	1.03	0.3090	0.3600	0.3107	0.3541
	pyroglutamylvaline	**1.20**	**1.19**	0.0309	0.0860	0.0362	0.0950
	cyclo(L-phe-L-pro)	1.15	0.97	0.2064	0.2817	0.2863	0.3398
	cyclo(gly-pro)	0.88	0.85	0.3180	0.3607	0.2410	0.3082
	cyclo(leu-pro)	1.08	0.95	0.5707	0.5120	0.7168	0.5527
	valylleucine	1.08	1.09	0.2227	0.2918	0.1920	0.2653
	aspartylleucine	0.64	0.64	0.3009	0.3553	0.3025	0.3517
	histidylalanine	1.48	1.41	0.3857	0.4048	0.5420	0.4940
	histidyltryptophan	0.63	0.63	0.1362	0.2179	0.1576	0.2389
	methionylalanine	3.67	3.50	0.2794	0.3440	0.3615	0.3854
	isoleucylalanine	**1.28**	**1.27**	0.0084	0.0327	0.0102	0.0357
	isoleucylglycine	1.11	1.11	0.1289	0.2090	0.1332	0.2170
	isoleucylphenylalanine	1.08	1.08	0.3871	0.4048	0.4099	0.4239
	isoleucylvaline	0.99	0.96	0.7009	0.5712	0.8037	0.5953
	leucylglutamate	**1.39**	**1.40**	0.0034	0.0171	0.0030	0.0163
	leucylglycine	0.94	0.92	0.6024	0.5229	0.6907	0.5436
	leucylphenylalanine	0.95	0.94	0.6139	0.5262	0.6768	0.5411
	phenylalanylleucine	0.49	0.50	0.7194	0.5761	0.7395	0.5663
	phenylalanylisoleucine	1.08	1.09	0.6440	0.5416	0.5404	0.4940
	serylleucine	1.27	1.26	0.1160	0.1936	0.1385	0.2204
	tryptophylleucine	0.92	0.92	0.2141	0.2862	0.1920	0.2653
	tryptophylasparagine	**3.58**	3.55	0.0967	0.1731	0.1234	0.2080
	tryptophylphenylalanine	1.09	1.08	0.1788	0.2608	0.2089	0.2841
	phenylalanyltryptophan	1.04	1.02	0.2361	0.3070	0.2710	0.3307
	tryptophylglutamate	**0.84**	**0.84**	0.0049	0.0220	0.0056	0.0245
Dipeptide derivative	carnosine	1.00	1.00				
	anserine	1.00	1.00				
	cys-gly, oxidized	**0.60**	**0.61**	0.0000	0.0006	0.0001	0.0010
	N-acetylcarnosine	1.00	0.99	0.9475	0.6338	0.9793	0.6394
gamma-glutamyl	gamma-glutamylvaline	**1.27**	**1.27**	0.0167	0.0521	0.0160	0.0520
	gamma-glutamyl-2-aminobutyrate	**0.88**	0.90	0.0622	0.1314	0.1087	0.1935
	gamma-glutamylleucine	0.99	1.00	0.6191	0.5294	0.8415	0.6068
	gamma-glutamylisoleucine	1.14	1.13	0.2069	0.2817	0.2561	0.3216
	gamma-glutamylmethionine	**0.68**	**0.69**	0.0000	0.0001	0.0000	0.0002
	gamma-glutamylglutamate	**1.31**	**1.33**	0.0510	0.1164	0.0328	0.0899
	gamma-glutamylglutamine	**0.71**	**0.72**	0.0002	0.0020	0.0003	0.0033

	gamma-glutamylphenylalanine	0.97	0.98	0.6137	0.5262	0.8137	0.5980
	gamma-glutamyltyrosine	0.97	0.99	0.5823	0.5137	0.8747	0.6151
	gamma-glutamyltryptophan	0.93	0.94	0.1146	0.1921	0.2219	0.2935
	gamma-glutamyllysine	1.03	1.04	0.9826	0.6437	0.8326	0.6064
	gamma-glutamylalanine	**0.64**	**0.65**	0.0000	0.0001	0.0000	0.0000
Polypeptide	bradykinin	1.13	1.06	0.3344	0.3721	0.2657	0.3290
	bradykinin, hydroxy-pro(3)	0.98	0.96	0.3153	0.3607	0.2670	0.3294
	bradykinin, des-arg(9)	1.19	1.09	0.3717	0.3958	0.2933	0.3434
	HXGXA	4.49	3.66	0.1757	0.2574	0.2753	0.3317
	HWESASXX	**5.25**	**4.81**	0.0000	0.0002	0.0000	0.0003
	XHWESASXXR	**68.71**	**22.31**	0.0019	0.0122	0.0034	0.0174
	HWESASLLR	**11.75**	**9.86**	0.0006	0.0053	0.0011	0.0086
Aminosugars metabolism	erythronate	1.03	1.02	0.5601	0.5080	0.6260	0.5300
	fucose	**1.35**	**1.34**	0.0154	0.0492	0.0187	0.0586
Fructose, mannose, galactose, starch, and sucrose metabolism	fructose	**0.78**	**0.79**	0.0137	0.0449	0.0195	0.0607
	maltose	1.57	1.55	0.2433	0.3117	0.2794	0.3351
	mannitol	1.07	1.04	0.8470	0.6152	0.7485	0.5707
	mannose	**1.33**	**1.34**	0.0012	0.0086	0.0009	0.0077
	sucrose	**0.52**	**0.52**	0.0024	0.0136	0.0022	0.0142
	methyl-beta-glucopyranoside	0.85	0.85	0.1953	0.2723	0.1836	0.2577
Glycolysis, gluconeogenesis, pyruvate metabolism	1,5-anhydroglucitol (1,5-AG)	1.06	1.07	0.3659	0.3921	0.2552	0.3216
	glycerate	1.03	1.03	0.8958	0.6221	0.9216	0.6280
	glucose	1.06	1.06	0.1385	0.2205	0.1294	0.2139
	1,6-anhydroglucose	**0.56**	**0.53**	0.0040	0.0184	0.0024	0.0145
	3-phosphoglycerate (isobar with 2-phosphoglycerate)	**1.76**	**1.75**	0.0520	0.1172	0.0636	0.1347
	pyruvate	**0.66**	**0.67**	0.0015	0.0102	0.0022	0.0143
	lactate	**0.69**	**0.69**	0.0000	0.0000	0.0000	0.0000
Glyoxylate and dicarboxylate metabolism	oxalate (ethanedioate)	**0.75**	**0.75**	0.0005	0.0047	0.0005	0.0046
Nucleotide sugars, pentose metabolism	arabitol	1.06	1.02	0.5994	0.5215	0.7627	0.5752
	threitol	**0.78**	**0.78**	0.0496	0.1147	0.0450	0.1080
	gluconate	**0.86**	**0.87**	0.0647	0.1320	0.0974	0.1799
	xylitol	2.14	1.14	0.1837	0.2614	0.3502	0.3791
	arabinose	1.00	0.95	0.7620	0.5843	0.5855	0.5163
	xylonate	1.00	1.00	0.8308	0.6085	0.8808	0.6158
Krebs cycle	citrate	0.95	0.94	0.4504	0.4511	0.4294	0.4388
	alpha-ketoglutarate	1.41	1.40	0.2064	0.2817	0.2300	0.2987
	succinate	**1.24**	**1.20**	0.0029	0.0156	0.0052	0.0239
	succinylcarnitine	1.11	1.07	0.3126	0.3607	0.4668	0.4593
	malate	**0.84**	**0.83**	0.0045	0.0206	0.0038	0.0193
Oxidative phosphorylation	acetylphosphate	1.08	1.08	0.1443	0.2256	0.1481	0.2315
	phosphate	1.04	1.04	0.3059	0.3588	0.2882	0.3409
Essential fatty acid	linoleate (18:2n6)	**1.48**	**1.48**	0.0004	0.0041	0.0005	0.0046
	linolenate [alpha or gamma; (18:3n3 or 6)]	**1.57**	**1.55**	0.0011	0.0086	0.0014	0.0104

	dihomo-linolenate (20:3n3 or n6)	1.50	1.49	0.0000	0.0005	0.0000	0.0007
	eicosapentaenoate (EPA; 20:5n3)	1.66	1.61	0.0016	0.0109	0.0023	0.0145
	docosapentaenoate (n3 DPA; 22:5n3)	1.86	1.83	0.0001	0.0011	0.0001	0.0015
	docosapentaenoate (n6 DPA; 22:5n6)	1.41	1.38	0.0022	0.0129	0.0029	0.0160
	docosahexaenoate (DHA; 22:6n3)	1.40	1.36	0.0125	0.0417	0.0177	0.0561
Short chain fatty acid	valerate	1.06	1.04	0.5901	0.5147	0.6654	0.5395
Medium chain fatty acid	caproate (6:0)	0.88	0.87	0.0102	0.0365	0.0062	0.0262
	caprylate (8:0)	0.73	0.72	0.0638	0.1318	0.0498	0.1148
	pelargonate (9:0)	0.89	0.88	0.0283	0.0791	0.0233	0.0676
	caprate (10:0)	0.90	0.88	0.7321	0.5764	0.6382	0.5351
	10-undecenoate (11:1n1)	1.65	1.66	0.0000	0.0003	0.0000	0.0003
	laurate (12:0)	1.24	1.21	0.0382	0.0983	0.0519	0.1171
	5-dodecenoate (12:1n7)	2.11	2.11	0.0000	0.0003	0.0000	0.0004
	2-aminoheptanoate	1.32	1.32	0.0010	0.0081	0.0009	0.0072
Long chain fatty acid	myristate (14:0)	1.49	1.46	0.0001	0.0009	0.0001	0.0014
	myristoleate (14:1n5)	2.41	2.38	0.0000	0.0001	0.0000	0.0001
	pentadecanoate (15:0)	1.51	1.50	0.0002	0.0017	0.0002	0.0024
	palmitate (16:0)	1.21	1.21	0.0029	0.0156	0.0039	0.0193
	palmitoleate (16:1n7)	1.94	1.90	0.0000	0.0002	0.0000	0.0003
	margarate (17:0)	1.25	1.23	0.0054	0.0239	0.0079	0.0316
	10-heptadecenoate (17:1n7)	1.84	1.80	0.0000	0.0004	0.0000	0.0005
	stearate (18:0)	1.20	1.19	0.0121	0.0410	0.0155	0.0515
	oleate (18:1n9)	1.75	1.73	0.0001	0.0009	0.0001	0.0012
	cis-vaccenate (18:1n7)	1.63	1.60	0.0005	0.0048	0.0007	0.0062
	stearidonate (18:4n3)	1.27	1.25	0.0409	0.1034	0.0497	0.1148
	10-nonadecenoate (19:1n9)	1.73	1.69	0.0001	0.0008	0.0001	0.0011
	eicosenoate (20:1n9 or 11)	1.51	1.48	0.0009	0.0075	0.0013	0.0098
	dihomo-linoleate (20:2n6)	1.42	1.39	0.0016	0.0109	0.0022	0.0142
	mead acid (20:3n9)	1.79	1.73	0.0000	0.0003	0.0000	0.0004
	arachidonate (20:4n6)	1.50	1.48	0.0001	0.0008	0.0001	0.0012
	docosadienoate (22:2n6)	1.31	1.26	0.0056	0.0239	0.0081	0.0319
	docosatrienoate (22:3n3)	1.36	1.28	0.0037	0.0179	0.0058	0.0248
	adrenate (22:4n6)	1.07	1.07	0.2144	0.2862	0.2418	0.3082
Fatty acid, methyl ester	palmitate, methyl ester	1.35	1.37	0.2995	0.3553	0.2915	0.3434
	margarate, methyl ester	1.14	1.16	0.5229	0.4893	0.4990	0.4746
	stearate, methyl ester	1.16	1.17	0.7419	0.5780	0.6988	0.5436
	oleate, methyl ester	1.31	1.33	0.4554	0.4530	0.4339	0.4416
	linoleate, methyl ester	1.14	1.16	0.5153	0.4861	0.4822	0.4653
Fatty acid, monohydroxy	3-hydroxypropanoate	0.91	0.90	0.2486	0.3173	0.2037	0.2802
	2-hydroxyoctanoate	1.08	1.08	0.4793	0.4674	0.5072	0.4774
	3-hydroxyoctanoate	1.11	1.11	0.2211	0.2918	0.2295	0.2987
	2-hydroxydecanoate	0.94	0.92	0.3355	0.3721	0.2756	0.3317
	3-hydroxydecanoate	1.36	1.37	0.0209	0.0631	0.0219	0.0663
	2-hydroxystearate	1.12	1.11	0.0224	0.0659	0.0279	0.0790
	2-hydroxypalmitate	1.24	1.23	0.0005	0.0048	0.0008	0.0065

	3-hydroxysebacate	1.24	1.24	0.4817	0.4685	0.5129	0.4788
	13-HODE + 9-HODE	**2.11**	**1.96**	0.0193	0.0592	0.0338	0.0914
Fatty acid, dicarboxylate	2-hydroxyglutarate	1.13	1.07	0.3506	0.3828	0.4714	0.4607
	suberate (octanedioate)	1.07	1.07	0.5879	0.5147	0.5967	0.5192
	azelate (nonanedioate)	**0.43**	**0.42**	0.0000	0.0000	0.0000	0.0000
	dodecanedioate	0.86	0.86	0.5090	0.4841	0.5008	0.4746
	octadecanedioate	0.91	0.91	0.8720	0.6190	0.9122	0.6265
	3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF)	1.24	1.22	0.4085	0.4183	0.3540	0.3821
Fatty acid, amino	2-aminooctanoate	1.08	1.09	0.7541	0.5817	0.6918	0.5436
Fatty acid, branched	15-methylpalmitate (isobar with 2-methylpalmitate)	**1.31**	**1.29**	0.0013	0.0094	0.0018	0.0119
Eicosanoid	leukotriene B4	1.03	1.01	0.1515	0.2348	0.3043	0.3527
	prostaglandin E2	2.15	1.95	0.5489	0.5055	0.3425	0.3767
	5-HETE	**1.04**	1.02	0.0966	0.1731	0.1672	0.2468
Endocannabinoid	N-stearoyltaurine	**1.34**	**1.32**	0.0038	0.0179	0.0057	0.0247
	N-palmitoyltaurine	**1.34**	**1.31**	0.0380	0.0983	0.0482	0.1133
Fatty acid metabolism (also BCAA metabolism)	propionylcarnitine	0.89	0.88	0.1670	0.2510	0.1592	0.2396
	butyrylcarnitine	**1.35**	**1.35**	0.0076	0.0303	0.0087	0.0330
	hydroxybutyrylcarnitine	**1.73**	**1.68**	0.0031	0.0163	0.0044	0.0210
	butyrylglycine	1.06	1.07	0.2828	0.3445	0.2595	0.3248
Fatty acid metabolism	valerylcarnitine	1.04	1.05	0.4635	0.4573	0.4230	0.4335
	isovalerate	**1.74**	1.45	0.0889	0.1650	0.1595	0.2396
Carnitine metabolism	deoxycarnitine	0.96	0.96	0.5830	0.5137	0.5357	0.4934
	carnitine	1.06	1.05	0.1202	0.1978	0.1411	0.2236
	acetylcarnitine	**1.21**	**1.20**	0.0032	0.0164	0.0048	0.0223
	hexanoylcarnitine	**1.12**	**1.13**	0.0235	0.0679	0.0204	0.0628
	2-methylmalonyl carnitine	1.01	1.01	0.8648	0.6190	0.8458	0.6074
	octanoylcarnitine	**1.07**	**1.08**	0.0436	0.1068	0.0363	0.0950
	decanoylcarnitine	**1.31**	**1.32**	0.0108	0.0374	0.0090	0.0334
	cis-4-decenoyl carnitine	**1.10**	**1.11**	0.0345	0.0919	0.0265	0.0756
	laurylcarnitine	**1.59**	**1.60**	0.0035	0.0174	0.0033	0.0172
	myristoylcarnitine	**1.48**	**1.49**	0.0093	0.0344	0.0100	0.0357
	palmitoylcarnitine	**1.22**	**1.22**	0.0661	0.1320	0.0720	0.1454
	stearoylcarnitine	1.09	1.09	0.2391	0.3077	0.2485	0.3143
	oleoylcarnitine	1.00	0.99	0.8009	0.5988	0.8620	0.6126
Bile acid metabolism	cholate	0.43	0.42	0.2727	0.3395	0.2444	0.3104
	glycocholate	**0.93**	**0.89**	0.0332	0.0907	0.0226	0.0669
	glycohyocholate	1.98	2.01	0.1244	0.2027	0.1275	0.2117
	taurocholate	2.37	2.31	0.3908	0.4054	0.3103	0.3541
	taurochenodeoxycholate	2.11	**2.07**	0.1103	0.1896	0.0813	0.1582
	taurodeoxycholate	**0.86**	**0.79**	0.0087	0.0333	0.0054	0.0244
	glycodeoxycholate	**0.67**	**0.61**	0.0007	0.0059	0.0004	0.0037
	glycochenodeoxycholate	**0.97**	**0.94**	0.0028	0.0152	0.0017	0.0118
	glycolithocholate sulfate	**0.96**	**0.95**	0.0886	0.1650	0.0782	0.1552
	taurolithocholate 3-sulfate	1.14	1.14	0.1827	0.2609	0.1715	0.2494

	glycocholenate sulfate	1.06	1.06	0.7705	0.5855	0.7895	0.5889
	taurocholenate sulfate	1.38	1.39	0.7134	0.5761	0.7093	0.5481
	glycoursodeoxycholate	**0.73**	**0.68**	0.0475	0.1128	0.0328	0.0899
	tauroursodeoxycholate	2.36	2.11	0.9807	0.6437	0.8303	0.6063
Glycerolipid metabolism	glycerol	**1.36**	**1.33**	0.0000	0.0003	0.0000	0.0005
	choline	**0.87**	**0.87**	0.0031	0.0163	0.0028	0.0157
	glycerol 3-phosphate (G3P)	1.22	1.24	0.5581	0.5080	0.5380	0.4940
	glycerophosphorylcholine (GPC)	**1.36**	**1.34**	0.0157	0.0496	0.0224	0.0667
	1-myristoleoylglycerophosphocholine (14:1)	1.13	1.09	0.7170	0.5761	0.8428	0.6068
Inositol metabolism	myo-inositol	1.00	1.00	0.8910	0.6221	0.9233	0.6280
	chiro-inositol	0.98	0.97	0.1825	0.2609	0.1521	0.2356
	scyllo-inositol	0.97	0.94	0.8841	0.6221	0.7856	0.5886
Ketone bodies	3-hydroxybutyrate (BHBA)	**2.19**	**2.19**	0.0065	0.0265	0.0081	0.0319
Lysolipid	1-palmitoylglycerophosphoethanolamine	1.08	1.06	0.3568	0.3859	0.4389	0.4431
	2-palmitoylglycerophosphoethanolamine	**1.17**	1.15	0.0860	0.1623	0.1074	0.1932
	1-palmitoleoylglycerophosphoethanolamine	1.27	1.23	0.5813	0.5137	0.6985	0.5436
	1-margaroylglycerophosphoethanolamine*	1.05	1.03	0.6118	0.5262	0.7093	0.5481
	1-stearoylglycerophosphoethanolamine	**1.18**	**1.16**	0.0656	0.1320	0.0893	0.1688
	2-stearoylglycerophosphoethanolamine	0.75	0.74	0.7373	0.5778	0.6789	0.5415
	1-oleoylglycerophosphoethanolamine	0.98	0.94	0.9215	0.6285	0.7525	0.5712
	2-oleoylglycerophosphoethanolamine	0.93	0.90	0.9821	0.6437	0.8641	0.6128
	1-linoleoylglycerophosphoethanolamine	0.93	0.92	0.5032	0.4804	0.4604	0.4570
	2-linoleoylglycerophosphoethanolamine	0.98	0.98	0.6275	0.5326	0.6006	0.5200
	1-arachidonoylglycerophosphoethanolamine	1.12	1.11	0.3453	0.3782	0.4075	0.4233
	2-arachidonoylglycerophosphoethanolamine	1.10	1.09	0.7402	0.5780	0.8126	0.5980
	2-docosahexaenoylglycerophosphoethanolamine	1.14	1.11	0.5409	0.5027	0.6370	0.5351
	1-myristoylglycerophosphocholine (14:0)	1.28	1.24	0.1746	0.2574	0.2277	0.2979
	2-myristoylglycerophosphocholine	**1.36**	**1.33**	0.0632	0.1314	0.0842	0.1607
	1-pentadecanoylglycerophosphocholine (15:0)	**1.18**	**1.17**	0.0507	0.1164	0.0573	0.1237
	1-palmitoylglycerophosphocholine (16:0)	1.04	1.04	0.3153	0.3607	0.3453	0.3786
	2-palmitoylglycerophosphocholine	1.16	1.16	0.1029	0.1795	0.1210	0.2050
	1-palmitoleoylglycerophosphocholine (16:1)	**1.27**	**1.24**	0.0487	0.1145	0.0685	0.1417
	2-palmitoleoylglycerophosphocholine	1.21	1.17	0.3810	0.4033	0.4812	0.4653
	1-margaroylglycerophosphocholine (17:0)	0.97	0.97	0.9534	0.6365	0.9618	0.6369
	1-stearoylglycerophosphocholine (18:0)	1.04	1.02	0.8669	0.6190	0.9443	0.6321
	2-stearoylglycerophosphocholine	0.94	0.93	0.9777	0.6437	0.9762	0.6394
	1-oleoylglycerophosphocholine (18:1)	1.07	1.06	0.4105	0.4191	0.4658	0.4593
	2-oleoylglycerophosphocholine	1.05	1.04	0.5118	0.4843	0.5754	0.5122
	1-linoleoylglycerophosphocholine (18:2n6)	0.97	0.97	0.7707	0.5855	0.7911	0.5889
	2-linoleoylglycerophosphocholine	0.98	0.98	0.8942	0.6221	0.9124	0.6265
	1-arachidoylglycerophosphocholine (20:0)	0.49	0.49	0.2733	0.3395	0.2740	0.3317
	1-dihomo-linoleoylglycerophosphocholine (20:2n6)	0.99	0.99	0.9464	0.6338	0.9707	0.6386
	1-eicosatrienoylglycerophosphocholine (20:3)	1.13	1.13	0.2097	0.2827	0.2193	0.2934
	2-eicosatrienoylglycerophosphocholine	**1.21**	**1.21**	0.0521	0.1172	0.0616	0.1314

	1-arachidonoylglycerophosphocholine (20:4n6)	1.13	1.12	0.1985	0.2757	0.2201	0.2934
	2-arachidonoylglycerophosphocholine	1.08	1.08	0.4988	0.4804	0.5407	0.4940
	1-docosapentaenoylglycerophosphocholine (22:5n3)	1.13	1.13	0.3160	0.3607	0.3388	0.3739
	1-docosahexaenoylglycerophosphocholine (22:6n3)	**1.21**	**1.19**	0.0632	0.1314	0.0799	0.1569
	2-docosahexaenoylglycerophosphocholine	1.15	1.13	0.2516	0.3200	0.2932	0.3434
	1-palmitoylglycerophosphoinositol	**1.27**	1.23	0.0777	0.1507	0.1030	0.1883
	1-stearoylglycerophosphoinositol	**1.24**	**1.21**	0.0312	0.0860	0.0419	0.1040
	2-stearoylglycerophosphoinositol	**1.22**	1.19	0.0894	0.1650	0.1155	0.1994
	1-oleoylglycerophosphoinositol	1.08	1.07	0.8549	0.6190	0.9357	0.6307
	1-linoleoylglycerophosphoinositol	1.09	1.09	0.6550	0.5466	0.6540	0.5390
	1-arachidonoylglycerophosphoinositol	**1.20**	**1.19**	0.0340	0.0919	0.0438	0.1074
	1-palmitoylplasmenylethanolamine	**1.42**	**1.39**	0.0093	0.0344	0.0136	0.0466
	1-arachidonoylglyercophosphate	0.76	0.74	0.7624	0.5843	0.6642	0.5395
	2-eicosapentaenoylglycerophosphoethanolamine	1.05	1.04	0.8571	0.6190	0.9027	0.6261
	1-eicosatrienoylglycerophosphoethanolamine	1.04	1.03	0.5255	0.4905	0.5671	0.5084
	1-docosahexaenoylglycerophosphoethanolamine	1.22	1.19	0.1204	0.1978	0.1577	0.2389
	1-linolenoylglycerophosphocholine (18:3n3)	0.94	0.94	0.7807	0.5879	0.7595	0.5740
	1-eicosenoylglycerophosphocholine (20:1n9)	0.93	0.92	0.9343	0.6307	0.8725	0.6150
	1-eicosapentaenoylglycerophosphocholine (20:5n3)	1.16	1.16	0.3348	0.3721	0.3489	0.3791
	1-oleoylplasmenylethanolamine	**1.36**	**1.34**	0.0347	0.0919	0.0463	0.1102
	1-eicosapentaenoylglycerophosphoethanolamine	0.93	0.92	0.8705	0.6190	0.8357	0.6064
	1-nonadecanoylglycerophosphocholine(19:0)	0.70	0.70	0.4958	0.4804	0.4760	0.4632
	2-linolenoylglycerophosphocholine(18:3n3)	1.09	1.08	0.6341	0.5370	0.6764	0.5411
	1-linolenoylglycerophosphoethanolamine (18:3n3)	0.88	0.87	0.7426	0.5780	0.6967	0.5436
Monoacylglycerol	1-stearoylglycerol (1-monostearin)	1.09	1.00	0.7933	0.5955	0.6541	0.5390
Sphingolipid	sphinganine	**1.96**	**1.97**	0.0095	0.0347	0.0094	0.0347
	sphingosine	1.63	1.64	0.3421	0.3770	0.3501	0.3791
	sphingosine 1-phosphate	**0.80**	**0.81**	0.0061	0.0258	0.0087	0.0330
	palmitoyl sphingomyelin	**1.15**	**1.16**	0.0526	0.1172	0.0407	0.1031
	stearoyl sphingomyelin	**1.36**	**1.37**	0.0035	0.0174	0.0025	0.0149
Sterol/Steroid	lathosterol	**1.23**	**1.22**	0.0471	0.1127	0.0512	0.1164
	cholesterol	**1.13**	**1.13**	0.0056	0.0239	0.0055	0.0244
	7-beta-hydroxycholesterol	**1.36**	**1.36**	0.0038	0.0179	0.0044	0.0210
	dehydroisoandrosterone sulfate (DHEA-S)	1.02	1.03	0.2825	0.3445	0.2856	0.3398
	epiandrosterone sulfate	0.92	0.93	0.1847	0.2617	0.2048	0.2807
	androsterone sulfate	1.08	1.10	0.8985	0.6221	0.9856	0.6407
	estrone 3-sulfate	**1.46**	**1.46**	0.0226	0.0659	0.0231	0.0675
	cortisol	0.88	0.88	0.1490	0.2320	0.1340	0.2173
	cortisone	1.14	1.14	0.3071	0.3590	0.3079	0.3537
	campesterol	1.08	1.08	0.3221	0.3607	0.3588	0.3844
	7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	**1.41**	**1.39**	0.0000	0.0003	0.0000	0.0004

	4-androsten-3beta,17beta-diol disulfate 1	1.04	1.00	0.5019	0.4804	0.5956	0.5192
	4-androsten-3beta,17beta-diol disulfate 2	0.98	0.99	0.9326	0.6307	0.9410	0.6321
	5alpha-androstan-3alpha,17beta-diol monosulfate 1	1.27	1.27	0.1124	0.1905	0.1211	0.2050
	5alpha-androstan-3beta,17beta-diol disulfate	0.71	0.70	0.9238	0.6289	0.8671	0.6137
	5alpha-pregnan-3beta,20alpha-diol disulfate	1.45	1.47	0.8171	0.6036	0.8697	0.6143
	5alpha-pregnan-3alpha,20beta-diol disulfate 1	1.40	1.42	0.9088	0.6235	0.9184	0.6280
	pregnen-diol disulfate	1.09	1.08	0.4080	0.4183	0.4538	0.4530
	pregn steroid monosulfate	1.02	1.02	0.5726	0.5123	0.5703	0.5090
	andro steroid monosulfate 1	1.55	1.57	0.1205	0.1978	0.1188	0.2042
	andro steroid monosulfate 2	1.53	1.55	0.1530	0.2361	0.1107	0.1945
	21-hydroxypregnenolone monosulfate 1	1.00	1.01	0.8350	0.6103	0.8978	0.6239
	21-hydroxypregnenolone disulfate	1.03	1.03	0.6420	0.5416	0.6636	0.5395
	5alpha-androstan-3beta,17alpha-diol disulfate	0.75	0.76	0.3453	0.3782	0.3729	0.3963
	5alpha-androstan-3alpha,17beta-diol disulfate	0.67	0.65	0.5900	0.5147	0.5206	0.4821
	pregnenolone sulfate	0.86	0.85	0.1427	0.2241	0.1203	0.2050
	pregnanediol-3-glucuronide	1.06	1.08	0.1856	0.2620	0.2181	0.2934
	5alpha-androstan-3beta,17beta-diol monosulfate 2	1.00	0.99	0.5428	0.5027	0.5874	0.5163
	5-pregnen-3b, 17-diol-20-one 3-sulfate	1.01	0.99	0.7285	0.5761	0.6425	0.5351
Glycerophosphodiester	1-palmitoylglycerophosphoglycerol	1.08	1.07	0.7677	0.5855	0.8547	0.6112
	1-stearoylglycerophosphoglycerol	**1.28**	1.22	0.0941	0.1711	0.1304	0.2144
Purine metabolism, (hypo)xanthine/inosine containing	xanthine	**1.62**	**1.55**	0.0006	0.0053	0.0010	0.0082
	xanthosine	**1.99**	**1.95**	0.0000	0.0002	0.0000	0.0003
	hypoxanthine	1.55	1.47	0.1885	0.2639	0.2251	0.2956
	inosine	**22.22**	11.42	0.0735	0.1449	0.1346	0.2173
	2'-deoxyinosine	1.00	1.00				
Purine metabolism, adenine containing	N1-methyladenosine	**1.18**	**1.18**	0.0000	0.0005	0.0000	0.0005
	N6-methyladenosine	**1.41**	**1.36**	0.0022	0.0129	0.0039	0.0195
	adenosine 5'-monophosphate (AMP)	**1.86**	**1.87**	0.0491	0.1145	0.0536	0.1182
	adenosine 5'-diphosphate (ADP)	**4.46**	**4.51**	0.0000	0.0000	0.0000	0.0000
Purine metabolism, guanine containing	7-methylguanine	**1.17**	**1.16**	0.0021	0.0129	0.0032	0.0171
	N1-methylguanosine	**1.47**	**1.47**	0.0000	0.0006	0.0000	0.0007
	N2,N2-dimethylguanosine	**1.13**	**1.12**	0.0122	0.0410	0.0151	0.0507
	N6-carbamoylthreonyladenosine	**1.15**	**1.15**	0.0020	0.0127	0.0028	0.0157
Purine metabolism, urate metabolism	urate	**1.12**	**1.11**	0.0271	0.0764	0.0362	0.0950
	allantoin	1.19	1.19	0.1051	0.1816	0.1109	0.1945
Pyrimidine metabolism, cytidine containing	N4-acetylcytidine	**1.22**	**1.21**	0.0414	0.1034	0.0523	0.1173
Pyrimidine metabolism, thymine containing	5,6-dihydrothymine	**1.75**	**1.78**	0.0000	0.0001	0.0000	0.0000
Pyrimidine metabolism, uracil containing	uridine	1.00	1.00	0.9082	0.6235	0.8356	0.6064
	pseudouridine	**1.09**	**1.09**	0.0085	0.0329	0.0102	0.0357
	5-methyluridine (ribothymidine)	0.99	0.99	0.8867	0.6221	0.8073	0.5958
Ascorbate and aldarate metabolism	threonate	**0.64**	**0.63**	0.0000	0.0005	0.0000	0.0004

Hemoglobin and porphyrin metabolism	heme	2.37	2.41	0.2085	0.2827	0.1807	0.2547
	L-urobilin	1.13	1.15	0.9885	0.6463	0.9664	0.6371
	bilirubin (Z,Z)	0.96	0.98	0.3912	0.4054	0.3595	0.3844
	bilirubin (E,E)	1.14	1.16	0.6521	0.5466	0.5967	0.5192
	bilirubin (E,Z or Z,E)	1.12	1.13	0.4793	0.4674	0.4347	0.4416
	biliverdin	**1.89**	**1.90**	0.0002	0.0025	0.0003	0.0029
	urobilinogen	0.95	0.94	0.8629	0.6190	0.8001	0.5943
Nicotinate and nicotinamide metabolism	nicotinamide	**1.61**	**1.62**	0.0958	0.1731	0.0960	0.1782
	nicotinurate	1.00	1.00				
	1-methylnicotinamide	1.69	1.70	0.4742	0.4651	0.4712	0.4607
	trigonelline (N'-methylnicotinate)	0.75	0.74	0.3871	0.4048	0.3582	0.3844
	N1-Methyl-2-pyridone-5-carboxamide	1.08	1.08	0.7942	0.5955	0.8049	0.5953
Pantothenate and CoA metabolism	pantothenate	1.31	1.29	0.1017	0.1783	0.1328	0.2170
Pyridoxal metabolism	pyridoxate	0.85	0.84	0.1819	0.2609	0.1566	0.2389
Riboflavin metabolism	riboflavin (Vitamin B2)	0.96	0.96	0.7316	0.5764	0.7448	0.5692
Tocopherol metabolism	alpha-tocopherol	1.19	1.20	0.5586	0.5080	0.5327	0.4920
	gamma-tocopherol	1.26	1.27	0.1352	0.2173	0.1258	0.2109
	gamma-CEHC	1.01	1.02	0.8819	0.6221	0.7881	0.5889
	gamma-CEHC glucuronide	1.04	1.05	0.6860	0.5647	0.6554	0.5390
Benzoate metabolism	hippurate	**0.50**	**0.50**	0.0103	0.0365	0.0099	0.0357
	3-methyl catechol sulfate 1	**0.72**	**0.72**	0.0527	0.1172	0.0468	0.1108
	3-methyl catechol sulfate 2	**0.67**	**0.67**	0.0845	0.1612	0.0830	0.1593
	4-methylcatechol sulfate	1.00	0.99	0.6850	0.5647	0.6430	0.5351
	2-hydroxyhippurate (salicylurate)	0.90	0.91	0.6778	0.5616	0.6216	0.5288
	3-hydroxyhippurate	0.90	0.90	0.4710	0.4632	0.4517	0.4523
	4-hydroxyhippurate	0.74	0.73	0.1826	0.2609	0.1550	0.2389
	catechol sulfate	0.81	0.81	0.1552	0.2383	0.1381	0.2204
	benzoate	0.94	0.94	0.6956	0.5692	0.6445	0.5351
	3-ethylphenylsulfate	1.56	1.58	0.9719	0.6415	0.9434	0.6321
	4-ethylphenylsulfate	1.19	1.20	0.5604	0.5080	0.5896	0.5169
	4-vinylphenol sulfate	0.91	0.90	0.9988	0.6494	0.9552	0.6357
	O-methylcatechol sulfate	0.89	0.88	0.2224	0.2918	0.1873	0.2620
Chemical	glycolate (hydroxyacetate)	**0.71**	**0.71**	0.0000	0.0000	0.0000	0.0000
	iminodiacetate (IDA)	0.95	0.96	0.4551	0.4530	0.5013	0.4746
	2-hydroxyisobutyrate	1.09	1.09	0.3008	0.3553	0.3246	0.3629
	glycerol 2-phosphate	1.28	1.29	0.5120	0.4843	0.4939	0.4746
	2-ethylhexanoate (isobar with 2-propylpentanoate)	2.39	2.41	0.5819	0.5137	0.5845	0.5163
	dexpanthenol	1.00	1.00				
	phenylcarnitine	1.11	1.11	0.3705	0.3958	0.4003	0.4202
	2-piperidinone	0.87	0.80	0.9580	0.6365	0.9236	0.6280
	dimethyl sulfone	0.91	0.91	0.5027	0.4804	0.5172	0.4804
	2-aminophenol sulfate	**0.70**	**0.71**	0.0222	0.0659	0.0305	0.0851
	O-sulfo-L-tyrosine	**1.11**	**1.12**	0.0646	0.1320	0.0534	0.1182
Drug	quetiapine	1.00	1.00				

	salicylate	1.26	1.28	0.7274	0.5761	0.6879	0.5436
	salicyluric glucuronide	1.27	1.28	0.8641	0.6190	0.8484	0.6080
	4-acetaminophen sulfate	0.25	0.20	0.7677	0.5855	0.6081	0.5211
	4-acetamidophenol	0.06	0.06	0.3542	0.3842	0.3237	0.3629
	p-acetamidophenylglucuronide	0.02	0.02	0.9045	0.6230	0.9665	0.6371
	2-hydroxyacetaminophen sulfate	0.89	0.89	0.5792	0.5137	0.5865	0.5163
	2-methoxyacetaminophen sulfate	0.93	0.91	0.8078	0.6005	0.6684	0.5400
	3-(cystein-S-yl)acetaminophen	1.35	1.30	0.8309	0.6085	0.6803	0.5415
	2-methoxyacetaminophen glucuronide	0.85	0.82	0.2870	0.3484	0.1682	0.2472
	4-acetylphenol sulfate	**0.51**	**0.51**	0.0062	0.0258	0.0055	0.0244
	ibuprofen	1.36	1.38	0.5844	0.5137	0.5682	0.5084
	carboxyibuprofen	0.93	0.94	0.6271	0.5326	0.6000	0.5200
	furosemide	1.00	1.00				
	naproxen	1.18	1.20	0.9356	0.6307	0.9195	0.6280
	desmethylnaproxen sulfate	1.13	1.13	0.4483	0.4511	0.4408	0.4431
	lidocaine	**1.21**	**1.21**	0.0662	0.1320	0.0661	0.1385
	metformin	1.00	1.01	0.7245	0.5761	0.7321	0.5624
	metoprolol	**1.05**	**1.05**	0.0931	0.1710	0.0931	0.1747
	metoprolol acid metabolite	**10.28**	**10.44**	0.0446	0.1083	0.0446	0.1079
	hydroquinone sulfate	0.68	0.68	0.1130	0.1905	0.1101	0.1945
	fexofenadine	0.98	0.98	0.8298	0.6085	0.8390	0.6068
	fluoxetine	1.00	1.00				
	norfluoxetine	1.00	1.00				
	6-oxopiperidine-2-carboxylic acid	**0.81**	**0.80**	0.0128	0.0424	0.0102	0.0357
	celecoxib	1.00	1.00				
	diphenhydramine	1.02	1.02	0.3214	0.3607	0.3215	0.3617
	ibuprofen acyl glucuronide	0.09	0.09	0.7522	0.5816	0.7327	0.5624
	pantoprazole	1.00	1.00				
	carbamazepine	1.00	1.00				
	carbamazepine 10,11-epoxide	1.00	1.00				
	hydrochlorothiazide	0.61	0.62	0.2611	0.3296	0.2691	0.3296
	carbamazepine glucuronide	1.00	1.00				
	gabapentin	1.00	1.00				
	benzoylecgonine	1.05	1.05	0.3214	0.3607	0.3215	0.3617
	meprobamate	1.00	1.00				
	paroxetine	1.00	1.00				
	atenolol	1.00	1.00				
	omeprazole	1.00	0.99	0.8631	0.6190	0.6634	0.5395
	escitalopram	1.10	1.11	0.6745	0.5602	0.6611	0.5395
	verapamil	1.00	1.00				
	quinine	1.00	1.00				
	oxypurinol	1.00	1.00				
	3-(N-acetyl-L-cystein-S-yl) acetaminophen	1.14	1.14	0.8037	0.5988	0.8270	0.6052
	2-hydroxyibuprofen	0.90	0.91	0.6968	0.5692	0.6706	0.5400
	desvenlafaxine	1.00	1.00	0.3214	0.3607	0.3215	0.3617

	norbenzoylecgonine	1.05	1.05	0.3214	0.3607	0.3215	0.3617
EDTA	EDTA	**1.16**	**1.16**	0.0000	0.0003	0.0000	0.0004
Food component/Plant	indoleacrylate	0.98	0.99	0.1877	0.2638	0.1651	0.2447
	saccharin	0.25	0.26	0.9260	0.6291	0.9594	0.6369
	quinate	0.86	0.85	0.2055	0.2817	0.1793	0.2544
	piperine	0.97	0.97	0.4636	0.4573	0.4406	0.4431
	dihydroferulic acid	1.23	1.22	0.2101	0.2827	0.1735	0.2507
	thymol sulfate	**0.54**	**0.53**	0.0855	0.1622	0.0717	0.1454
	ergothioneine	0.96	0.97	0.5205	0.4883	0.5489	0.4976
	N-(2-furoyl)glycine	**0.48**	**0.48**	0.0092	0.0344	0.0082	0.0319
	stachydrine	**0.79**	**0.76**	0.0457	0.1101	0.0342	0.0915
	homostachydrine	1.42	1.43	0.2209	0.2918	0.2209	0.2934
	4-hydroxyproline betaine	0.79	0.79	0.2551	0.3233	0.2321	0.3002
	cinnamoylglycine	1.10	1.11	0.9179	0.6285	0.8604	0.6126
	sucralose	**0.28**	**0.26**	0.0488	0.1145	0.0377	0.0977
Xanthine metabolism	caffeine	1.06	0.96	0.8133	0.6020	0.9097	0.6265
	paraxanthine	1.02	1.03	0.8960	0.6221	0.9094	0.6265
	theobromine	**1.49**	**1.47**	0.0578	0.1254	0.0652	0.1374
	theophylline	1.14	1.10	0.4170	0.4221	0.4722	0.4607
	1-methylurate	0.95	0.96	0.6589	0.5485	0.6711	0.5400
	1,3-dimethylurate	1.03	1.04	0.7578	0.5833	0.6964	0.5436
	1,7-dimethylurate	1.30	1.31	0.4161	0.4221	0.4167	0.4296
	3,7-dimethylurate	**1.50**	**1.52**	0.0540	0.1193	0.0430	0.1060
	1,3,7-trimethylurate	1.02	1.02	0.8035	0.5988	0.7843	0.5886
	1-methylxanthine	0.76	0.77	0.3973	0.4093	0.4081	0.4233
	3-methylxanthine	1.26	1.23	0.2393	0.3077	0.2741	0.3317
	7-methylxanthine	1.13	1.14	0.3940	0.4071	0.4066	0.4233
	5-acetylamino-6-amino-3-methyluracil	0.73	0.74	0.2966	0.3551	0.3079	0.3537
	7-methylurate	**1.41**	**1.41**	0.0077	0.0303	0.0076	0.0310
Tobacco metabolite	cotinine	0.73	0.74	0.8411	0.6134	0.8773	0.6151
	hydroxycotinine	1.32	1.34	0.8967	0.6221	0.9289	0.6303
	cotinine N-oxide	0.88	0.89	0.9318	0.6307	0.9626	0.6369
Sugar, sugar substitute, starch	erythritol	1.41	1.40	0.8870	0.6221	0.9772	0.6394
Detoxification metabolism	ethyl glucuronide	1.98	1.24	0.2882	0.3486	0.4413	0.4431

Quantification of specific pathway metabolites were assessed by ultrahigh performance liquid chromatography/mass spectrometry (UPLC/MS/MS) accompanied by gas chromatography/mass spectrometry (GC/MS). Results represented as ratios for comparison between psoriasis (n=60) vs. healthy plasma (n=30). Green: indicates significant difference ($p \leq 0.05$) between the groups shown, metabolite ratio of < 1.00; Light Green: narrowly missed statistical cutoff for significance $0.05 < p < 0.10$, metabolite ratio of < 1.00; Red: indicates significant difference ($p \leq 0.05$) between the groups shown; metabolite ratio of ≥ 1.00; Light Red: narrowly missed statistical cutoff for significance $0.05 < p < 0.10$, metabolite ratio of ≥ 1.00; Non-colored text and cell: mean values are not significantly different for that comparison. P values were derived from Welch's t-test.